# Analysis report (Supporting information)

Effect of oral nutritional supplements with or without nutritional counselling on mortality, treatment tolerance, and quality of life in head and neck cancer patients receiving (chemo)radiotherapy: a systematic review and meta-analysis

*Mello et al. (2020)*

## Contents

# 1 Abbreviations

**CCRT:** concurrent chemo-radiotherapy

**CI:** confidence interval

**CT:** chemotherapy

**MD:** mean difference

**MID:** minimal important difference

**NC:** nutritional counselling

**ONS:** oral nutritional supplements

**RR:** risk ratio

**RT:** radiotherapy

**SD:** standard deviation

**seTE:** standard error

**SMD:** standardized mean difference

**TE:** estimated treatment effect

# 2 Packages

```
library(meta)
```

```
## Loading 'meta' package (version 4.9-7).
## Type 'help(meta)' for a brief overview.
```

```
library(readr)
library(rmeta)
library(devtools)
```

```
## Loading required package: usethis
```

```
library(robvis)
library(patchwork)
library(ggplot2)
library(tidyr)
```

# 3 Standard configurations for the meta-analyses

```
settings.meta(hakn = TRUE) # Hartung-Knapp adjustment
```

```
Parsed with column specification:
cols(
  .default = col_double(),
  outclab = col_character(),
  D1 = col_character(),
  D2 = col_character(),
  D3 = col_character(),
  D4 = col_character(),
  D5 = col_character(),
  Overall = col_character(),
  bias = col_character(),
  site = col_character(),
  studlab = col_character(),
  X23 = col_logical()
)
```

```
See spec(...) for full column specifications.
```

# 4 Comparison 1

## 4.1 Mortality

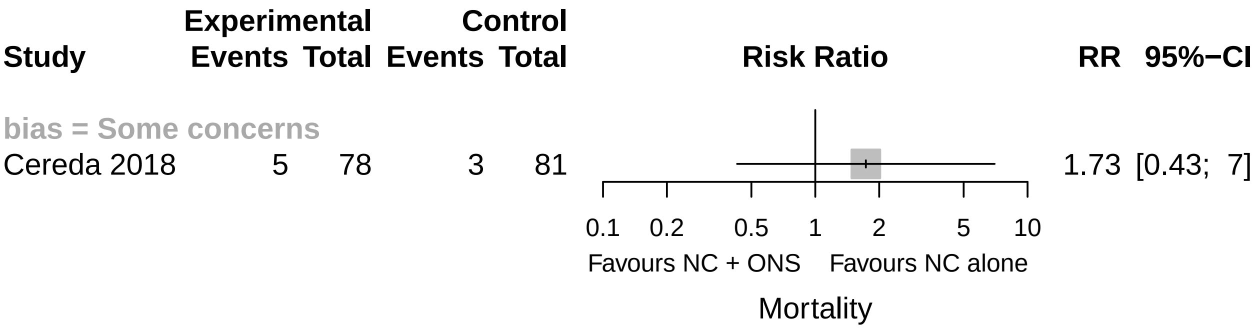
### 4.1.1 Main analysis

Including only results at most at some concerns of bias.

#### 4.1.1.1 Forest plot

```
mort_1_S <- metabin(
  HNC$event.e,
  HNC$n.e,
  HNC$event.c,
  HNC$n.c,
  sm = "RR",
  method = "MH",
  RR.cochrane = TRUE,
  MH.exact = FALSE,
  allstudies = FALSE,
  HNC$studlab,
  subset = HNC$outclab == "Mortality" & HNC$C == 1 & HNC$studlab == "Cereda 2018",
  exclude = HNC$studlab == "Jiang 2019",
  hakn = TRUE,
  byvar = HNC$bias
)
```

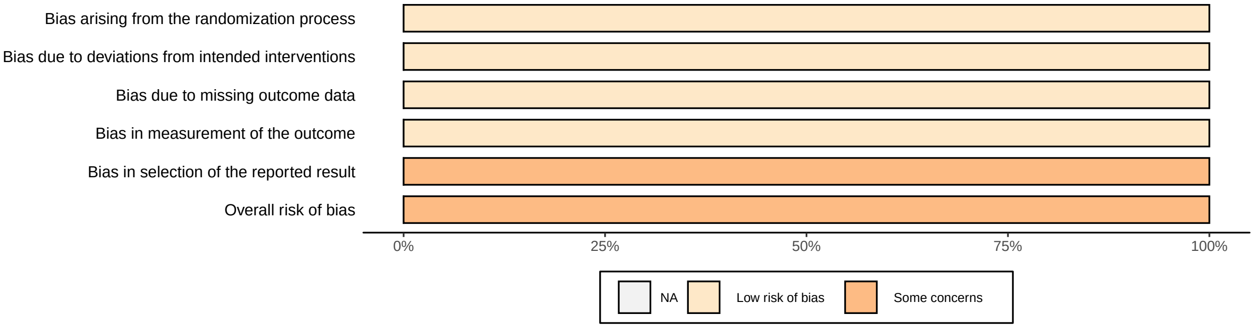
```r
mort_1_Sd <- data.frame(mort_1_S)
rob_mort_1_S <- subset(rob_mort_1, studlab == "Cereda 2018")
rob_mort_1_S <- merge(rob_mort_1_S, mort_1_Sd[,c("w.random", "studlab")], by = "studlab", all = TRUE)
rob_mort_1_S <- rob_mort_1_S[1:3,]

forest(mort_1_S,
       xlab="Mortality",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 2,
       comb.fixed = FALSE,
       xlim = c(0.1, 10),
       #plotwidth = "2cm",
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = TRUE,
       pooled.events = TRUE,
       resid.hetstat = FALSE,
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = C1,
       label.left = I1,
       fs.axis = 10,
       fs.lr = 10
)
```



#### 4.1.1.2 Proportion of information at each level of risk of bias

Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)

```r
rob_summary(rob_mort_1_S, tool = "ROB2", weighted = TRUE, overall = TRUE, colour = "colourblind")
```



### 4.1.2 Sensitivity analysis

Including all available results.

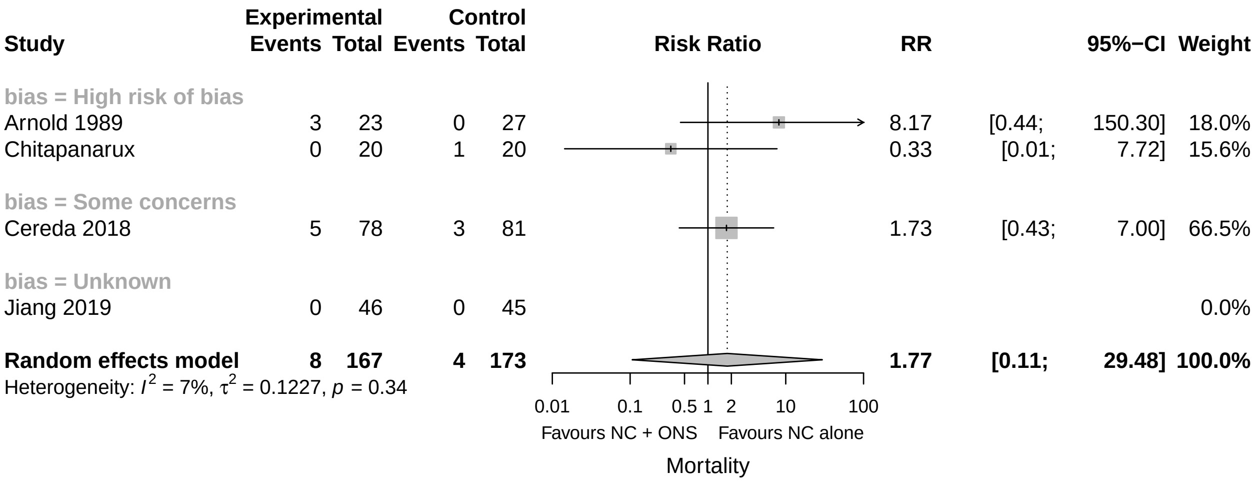
#### 4.1.2.1 Forest plot

```
mort_1 <- metabin(
  HNC$event.e,
  HNC$n.e,
  HNC$event.c,
  HNC$n.c,
  sm = "RR",
  method = "MH",
  RR.cochrane = TRUE,
  MH.exact = FALSE,
  allstudies = FALSE,
  HNC$studlab,
  subset = HNC$outclab == "Mortality" & HNC$C == 1,
  exclude = HNC$studlab == "Jiang 2019",
  hakn = TRUE,
  byvar = HNC$bias
)
```

```
## Warning in qt(1 - alpha/2, df = df): NaNs produzidos

## Warning in qt(1 - alpha/2, df = df): NaNs produzidos
```

```
mort_1d <- data.frame(mort_1)
rob_mort_1 <- merge(rob_mort_1, mort_1d[,c("w.random", "studlab")], by = "studlab", all = TRUE)
rob_mort_1 <- rob_mort_1[1:3,]

forest(mort_1,
       xlab="Mortality",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 2,
       comb.fixed = FALSE,
       xlim = c(0.01, 100),
       #plotwidth = "2cm",
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = TRUE,
       pooled.events = TRUE,
```

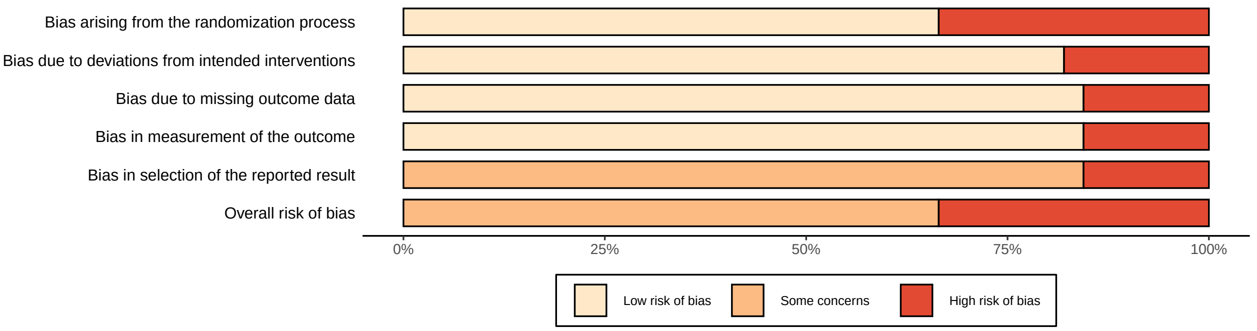
```
       resid.hetstat = FALSE,
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = C1,
       label.left = I1,
       fs.axis = 10,
       fs.lr = 10
)
```



### 4.1.2.2 Proportion of information at each level of risk of bias

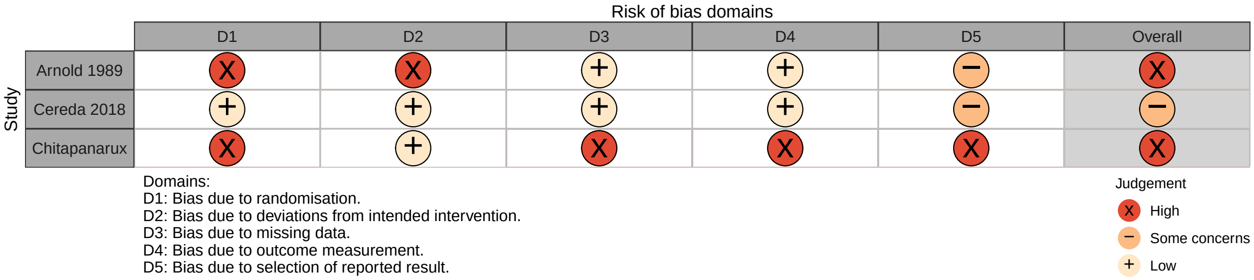
Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)

```
rob_summary(rob_mort_1, tool = "ROB2", weighted = TRUE, overall = TRUE, colour = "colourblind")
```



### 4.1.2.3 Risk of bias assessments by study

```
rob_traffic_light(rob_mort_1, tool = "ROB2", colour = "colourblind", psize = 10)
```



```
#forest(metainf(mort_1,
#               pooled = "random"))
```

## 4.2 Treatment tolerance

### 4.2.1 RT Complete suspension

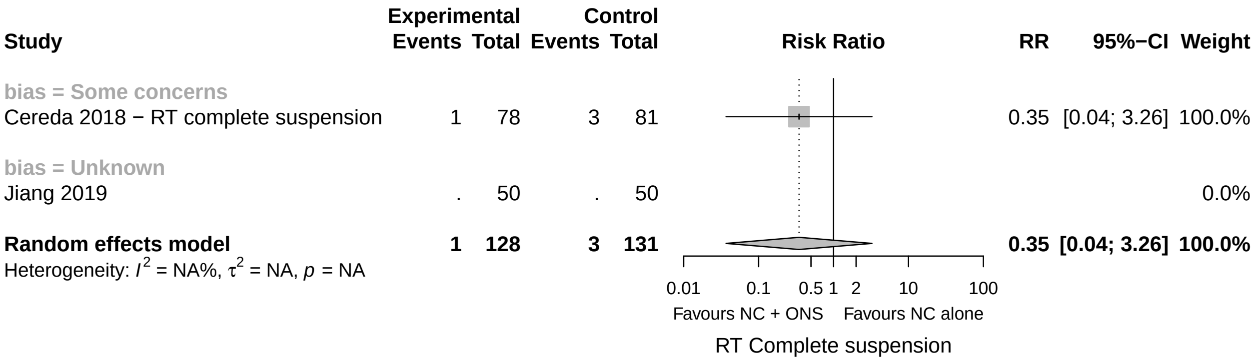
#### 4.2.1.1 Forest plot

```
rt_susp <- metabin(
  HNC$event.e,
  HNC$n.e,
  HNC$event.c,
  HNC$n.c,
  sm = "RR",
  method = "MH",
  RR.cochrane = TRUE,
  MH.exact = TRUE,
  allstudies = FALSE,
  HNC$studlab,
  subset = HNC$outclab == "RT_Susp" & HNC$C == 1,
  byvar = HNC$bias,
  comb.fixed = FALSE,
  comb.random = TRUE,
)
```

```
## Warning: For a single study, inverse variance method used instead of Mantel-
## Haenszel method.
```

```
rt_susp_d <- data.frame(rt_susp)
rob_rt_susp_1 <- merge(rob_rt_susp_1, rt_susp_d[,c("w.random", "studlab")], by = "studlab", all = TRUE)
rob_rt_susp_1_x <- subset(rob_rt_susp_1, studlab != "Jiang 2019")

forest(rt_susp,
       xlab="RT Complete suspension",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 2,
       digits.se = 1,
       comb.fixed = FALSE,
       pooled.events = TRUE,
       #overall = FALSE,
       subgroup = FALSE,
       hetstat = FALSE,
```

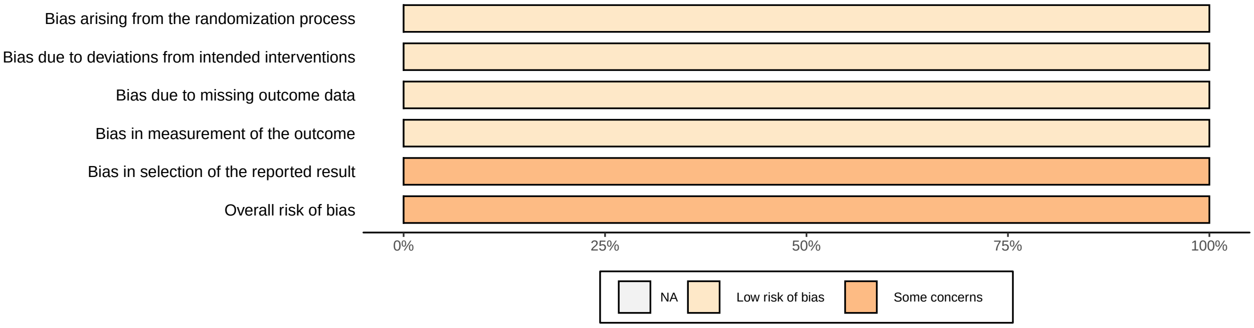
```
        overall.hetstat = TRUE,
        xlim = c(0.01, 100),
        #xlim    = "s",
        #plotwidth = "2cm",
        colgap.forest = "0.5 cm",
        just = "right",
        label.right = C1,
        label.left = I1,
        fs.axis = 10,
        fs.lr = 10
)
```



#### 4.2.1.2 Proportion of information at each level of risk of bias

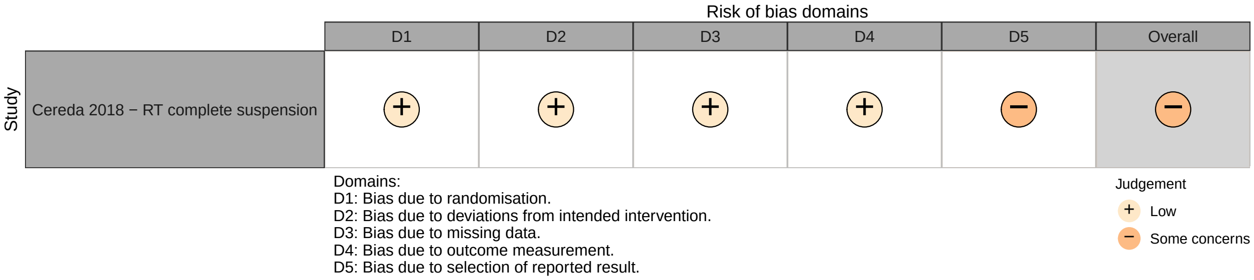
Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)

```
rob_summary(rob_rt_susp_1, tool = "ROB2", weighted = TRUE, overall = TRUE, colour = "colourblind")
```



#### 4.2.1.3 Risk of bias assessments by study

```
rob_traffic_light(rob_rt_susp_1_x, tool = "ROB2", colour = "colourblind", psize = 10)
```

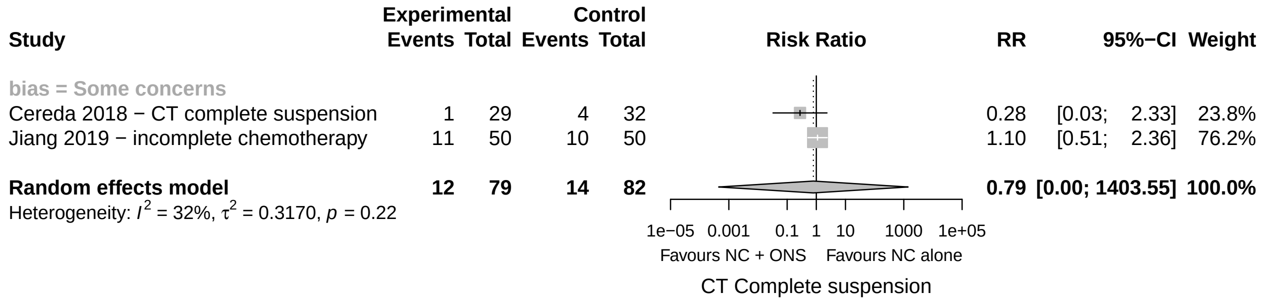


### 4.2.2 CT Complete suspension

#### 4.2.2.1 Forest plot

```
ct_susp <- metabin(
  HNC$event.e,
  HNC$n.e,
  HNC$event.c,
  HNC$n.c,
  sm = "RR",
  method = "MH",
  RR.cochrane = TRUE,
  MH.exact = TRUE,
  allstudies = TRUE,
  HNC$studlab,
  subset = HNC$outclab == "CT_Susp" & HNC$C == 1,
  byvar = HNC$bias,
  comb.fixed = FALSE,
  comb.random = TRUE,
)

ct_susp_d <- data.frame(ct_susp)
rob_ct_susp_1 <- merge(rob_ct_susp_1, ct_susp_d[,c("w.random", "studlab")], by = "studlab", all = TRUE)

forest(ct_susp,
       xlab="CT Complete suspension",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 2,
       digits.se = 1,
       comb.fixed = FALSE,
       pooled.events = TRUE,
       #overall = FALSE,
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = TRUE,
       xlim = c(0.00001, 100000),
       #xlim    = "s",
       #plotwidth = "2cm",
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = C1,
```

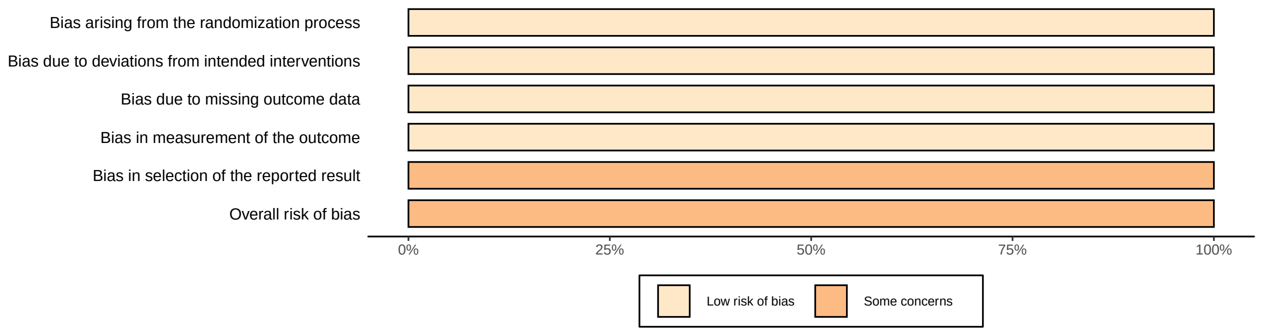
```
       label.left = I1,
       fs.axis = 10,
       fs.lr = 10
)
```



#### 4.2.2.2 Proportion of information at each level of risk of bias

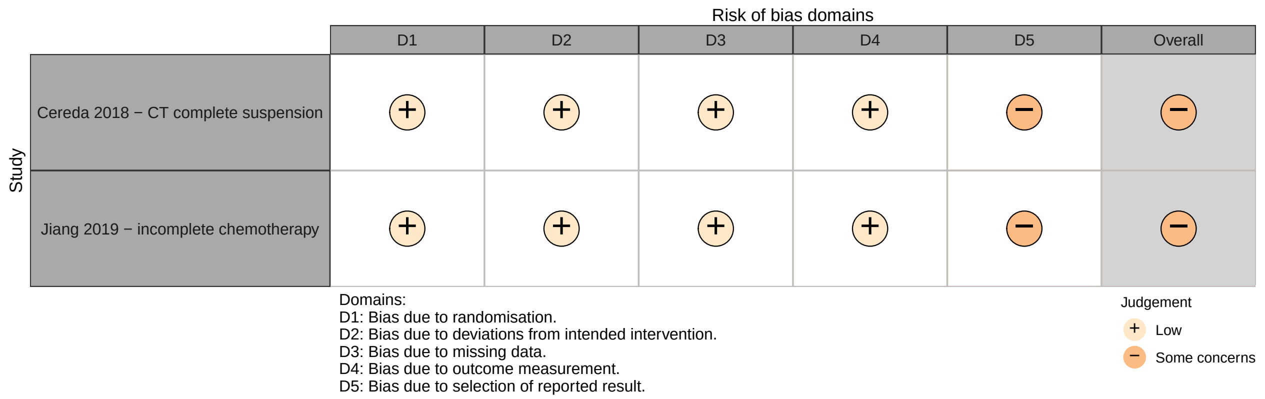
Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)

```
rob_summary(rob_ct_susp_1, tool = "ROB2", weighted = TRUE, overall = TRUE, colour = "colourblind")
```



#### 4.2.2.3 Risk of bias assessments by study

```
rob_traffic_light(rob_ct_susp_1, tool = "ROB2", colour = "colourblind", psize = 10)
```



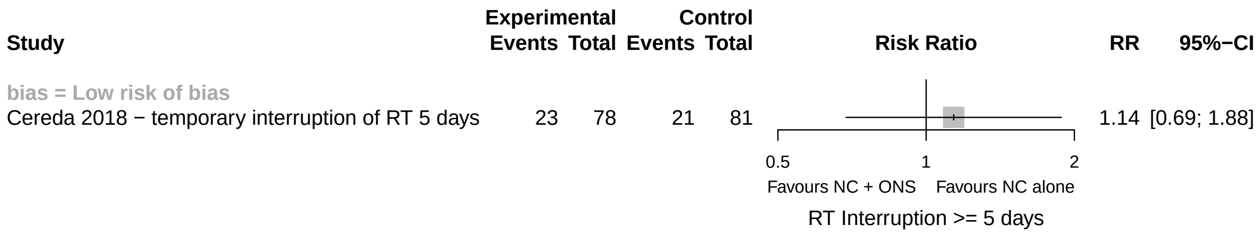
| Study | D1 | D2 | D3 | D4 | D5 | Overall |
|---|---|---|---|---|---|---|
| Cereda 2018 − CT complete suspension | + | + | + | + | − | − |
| Jiang 2019 − incomplete chemotherapy | + | + | + | + | − | − |

Domains:
D1: Bias due to randomisation.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing data.
D4: Bias due to outcome measurement.
D5: Bias due to selection of reported result.

### 4.2.3 RT interruption >= 5 days

#### 4.2.3.1 Forest plot

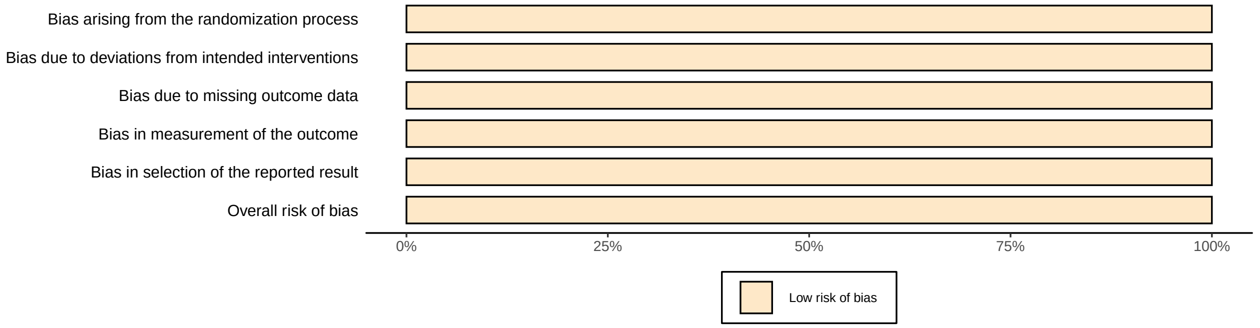
```
rt_int5 <- metabin(
  HNC$event.e,
  HNC$n.e,
  HNC$event.c,
  HNC$n.c,
  sm = "RR",
  method = "MH",
  RR.cochrane = TRUE,
  MH.exact = TRUE,
  allstudies = TRUE,
  HNC$studlab,
  subset = HNC$outclab == "Interruption" & HNC$C == 1,
  byvar = HNC$bias,
  comb.fixed = FALSE,
  comb.random = TRUE,
)

rt_int5_d <- data.frame(rt_int5)
rob_rt_int5_1 <- merge(rob_rt_int5_1, rt_int5_d[,c("w.random", "studlab")], by = "studlab", all = TRUE)

forest(rt_int5,
       xlab="RT Interruption >= 5 days",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 2,
       digits.se = 1,
       comb.fixed = FALSE,
       pooled.events = TRUE,
       #overall = FALSE,
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = TRUE,
       xlim = c(0.5, 2),
       #xlim    = "s",
       #plotwidth = "2cm",
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = C1,
       label.left = I1,
       fs.axis = 10,
       fs.lr = 10
)
```



### 4.2.3.2 Proportion of information at each level of risk of bias

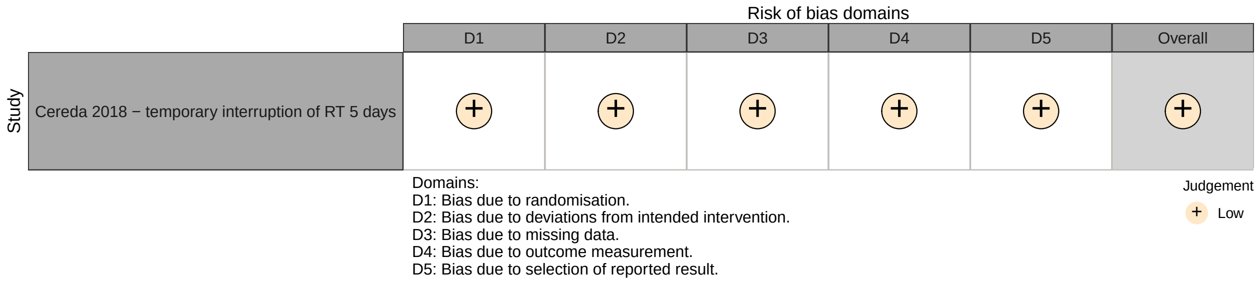
Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)

```r
rob_summary(rob_rt_int5_1, tool = "ROB2", weighted = TRUE, overall = TRUE, colour = "colourblind")
```



### 4.2.3.3 Risk of bias assessments by study

```r
rob_traffic_light(rob_rt_int5_1, tool = "ROB2", colour = "colourblind", psize = 10)
```



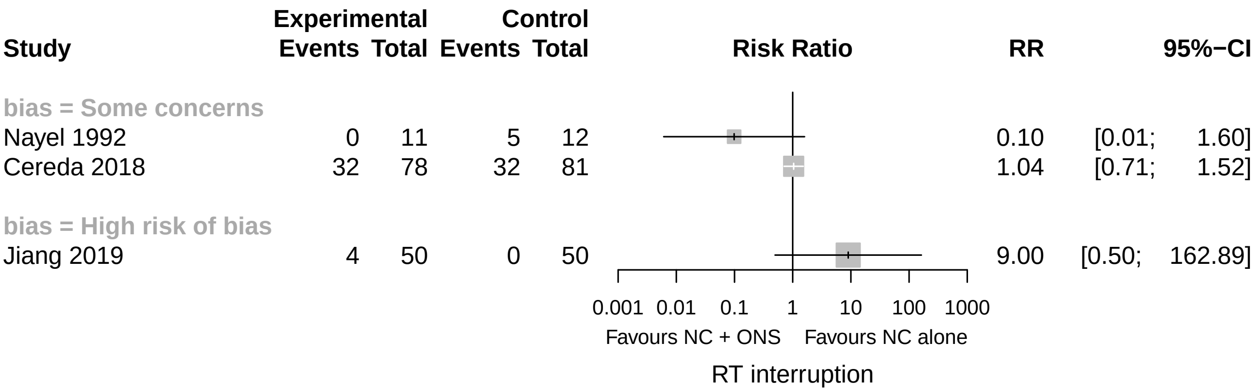
Domains:
D1: Bias due to randomisation.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing data.
D4: Bias due to outcome measurement.
D5: Bias due to selection of reported result.

### 4.2.4 RT interruption

### 4.2.4.1 Forest plot

```r
rt_int <- metabin(
  HNC$event.e,
  HNC$n.e,
  HNC$event.c,
  HNC$n.c,
  sm = "RR",
  method = "MH",
  RR.cochrane = TRUE,
  MH.exact = TRUE,
```

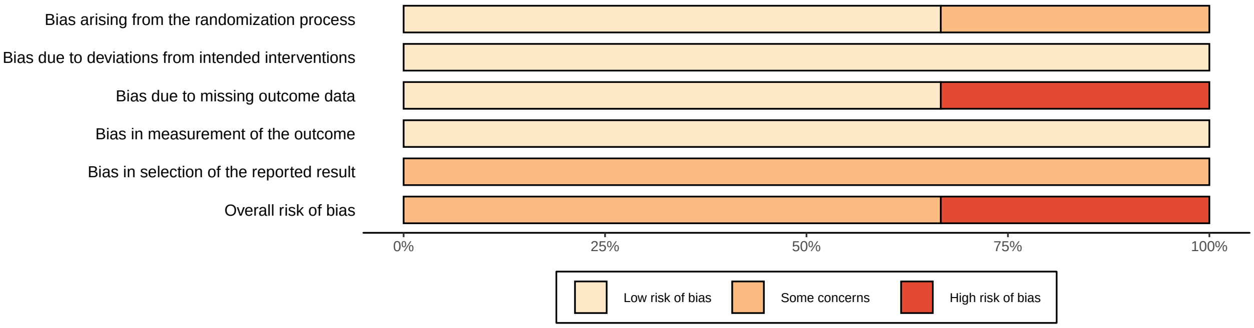
```
  #allstudies = TRUE,
  HNC$studlab,
  subset = HNC$outclab == "RT_Interruption" & HNC$C == 1,
  byvar = HNC$bias,
  comb.fixed = FALSE,
  comb.random = TRUE,
)

rt_int_d <- data.frame(rt_int)
rob_rt_int_1 <- merge(rob_rt_int_1, rt_int_d[,c("w.random", "studlab")], by = "studlab", all = TRUE)

forest(rt_int,
       xlab="RT interruption",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 2,
       digits.se = 1,
       comb.fixed = FALSE,
       pooled.events = TRUE,
       #overall = FALSE,
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = FALSE,
       overall = FALSE,
       xlim = c(0.001, 1000),
       #xlim    = "s",
       #plotwidth = "2cm",
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = C1,
       label.left = I1,
       fs.axis = 10,
       fs.lr = 10
)
```



#### 4.2.4.2 Proportion of information at each level of risk of bias

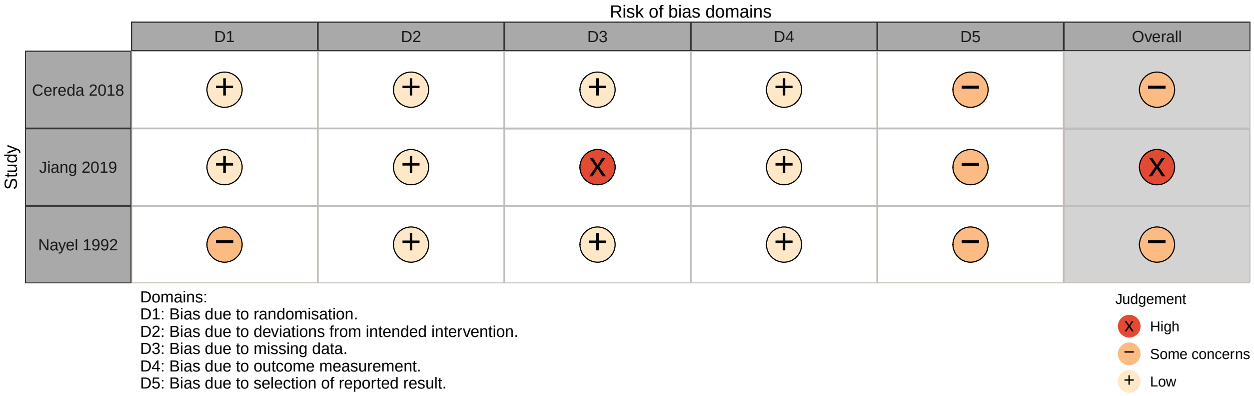
Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)

```
rob_summary(rob_rt_int_1, tool = "ROB2", weighted = FALSE, overall = TRUE, colour = "colourblind")
```



#### 4.2.4.3 Risk of bias assessments by study

```
rob_traffic_light(rob_rt_int_1, tool = "ROB2", colour = "colourblind", psize = 10)
```

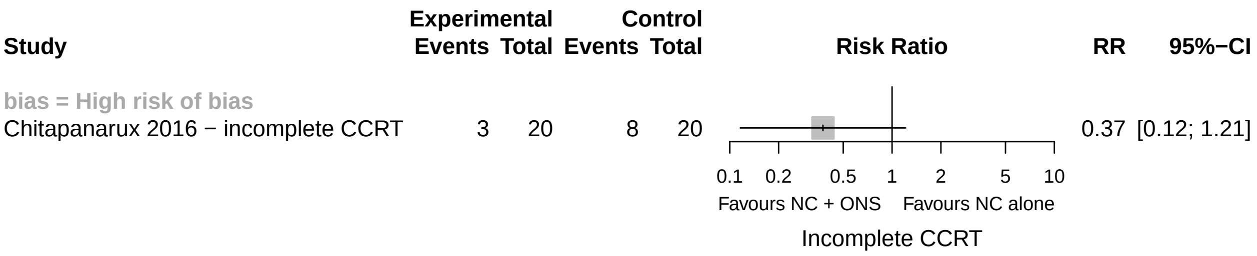


### 4.2.5 Incomplete CCRT

#### 4.2.5.1 Forest plot

```
ccrt_inc <- metabin(
  HNC$event.e,
  HNC$n.e,
  HNC$event.c,
  HNC$n.c,
  sm = "RR",
  method = "MH",
  RR.cochrane = TRUE,
  MH.exact = TRUE,
  #allstudies = TRUE,
  HNC$studlab,
  subset = HNC$outclab == "CCRT_Incomplete" & HNC$C == 1,
  byvar = HNC$bias,
  comb.fixed = FALSE,
  comb.random = TRUE,
)
```

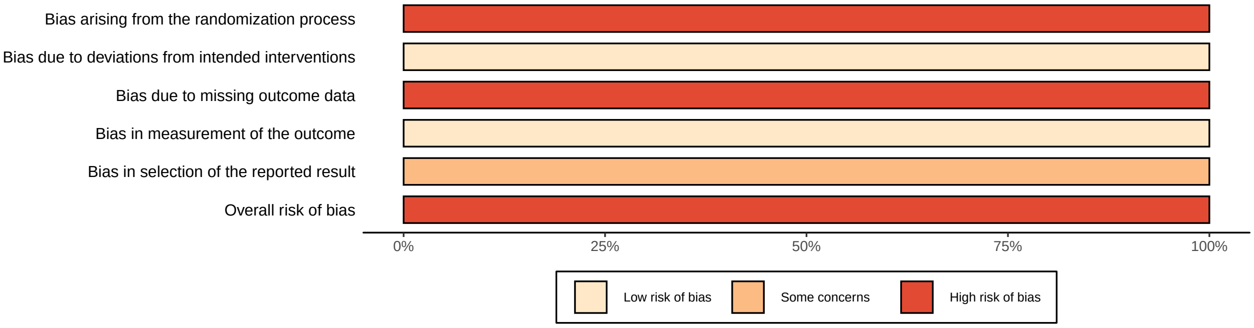
```
ccrt_inc_d <- data.frame(ccrt_inc)
rob_ccrt_inc_1 <- merge(rob_ccrt_inc_1, ccrt_inc_d[,c("w.random", "studlab")], by = "studlab", all = TRU

forest(ccrt_inc,
       xlab="Incomplete CCRT",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 2,
       digits.se = 1,
       comb.fixed = FALSE,
       pooled.events = TRUE,
       #overall = FALSE,
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = TRUE,
       xlim = c(0.1, 10),
       #xlim    = "s",
       #plotwidth = "2cm",
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = C1,
       label.left = I1,
       fs.axis = 10,
       fs.lr = 10
)
```



#### 4.2.5.2 Proportion of information at each level of risk of bias

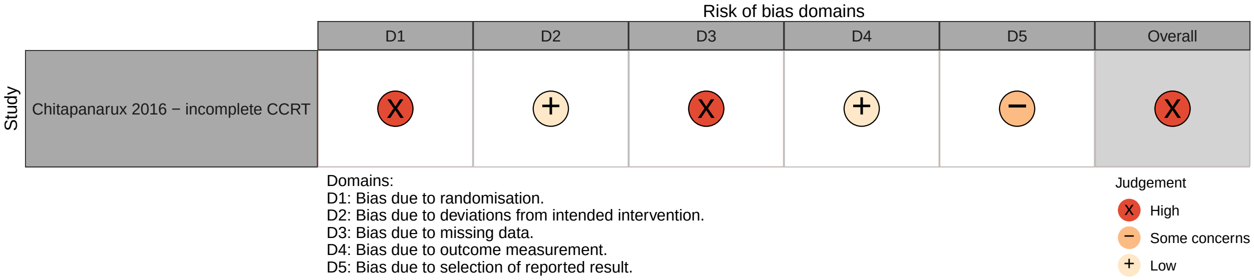
Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)

```
rob_summary(rob_ccrt_inc_1, tool = "ROB2", weighted = TRUE, overall = TRUE, colour = "colourblind")
```



#### 4.2.5.3 Risk of bias assessments by study

```
rob_traffic_light(rob_ccrt_inc_1, tool = "ROB2", colour = "colourblind", psize = 10)
```

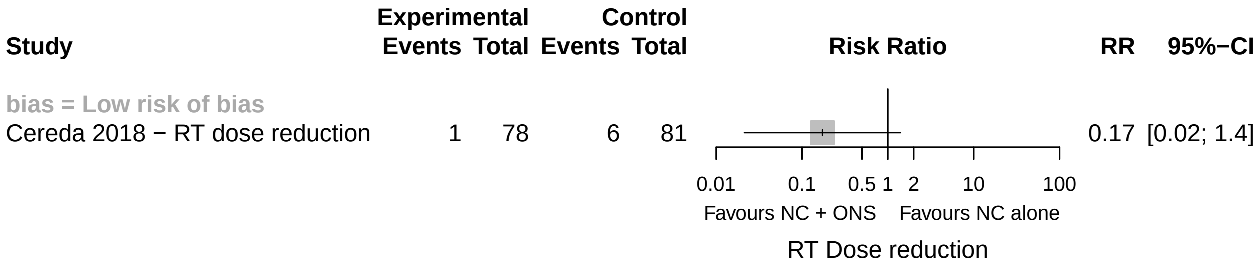


### 4.2.6 RT Dose reduction

#### 4.2.6.1 Forest plot

```
rt_dose <- metabin(
  HNC$event.e,
  HNC$n.e,
  HNC$event.c,
  HNC$n.c,
  sm = "RR",
  method = "MH",
  RR.cochrane = TRUE,
  MH.exact = TRUE,
  #allstudies = TRUE,
  HNC$studlab,
  subset = HNC$outclab == "RT_Dose" & HNC$C == 1,
  byvar = HNC$bias,
  comb.fixed = FALSE,
  comb.random = TRUE,
)

rt_dose_d <- data.frame(rt_dose)
rob_rt_dose_1 <- merge(rob_rt_dose_1, rt_dose_d[,c("w.random", "studlab")], by = "studlab", all = TRUE)

forest(rt_dose,
       xlab="RT Dose reduction",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 2,
       digits.se = 1,
       comb.fixed = FALSE,
       pooled.events = TRUE,
       #overall = FALSE,
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = TRUE,
       xlim = c(0.01, 100),
       #xlim    = "s",
```

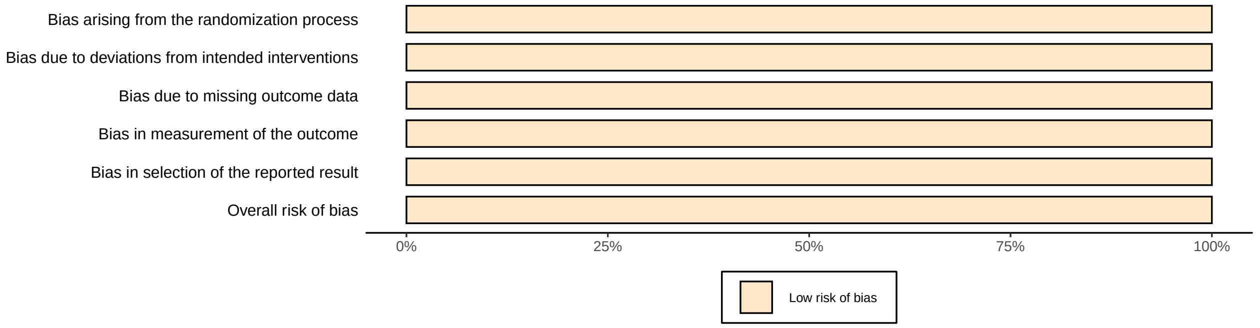
```
        #plotwidth = "2cm",
        colgap.forest = "0.5 cm",
        just = "right",
        label.right = C1,
        label.left = I1,
        fs.axis = 10,
        fs.lr = 10
)
```



### 4.2.6.2 Proportion of information at each level of risk of bias

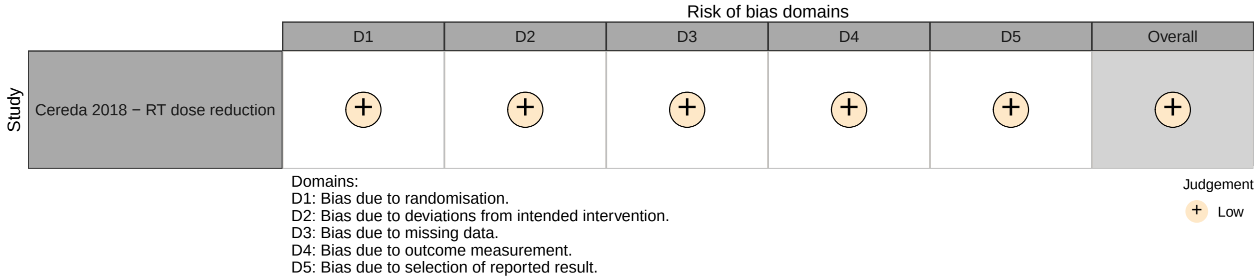
Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)

```
rob_summary(rob_rt_dose_1, tool = "ROB2", weighted = TRUE, overall = TRUE, colour = "colourblind")
```



### 4.2.6.3 Risk of bias assessments by study

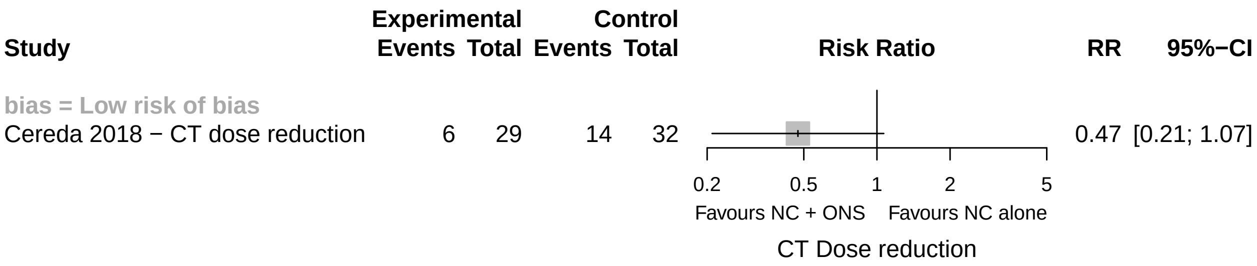
```
rob_traffic_light(rob_rt_dose_1, tool = "ROB2", colour = "colourblind", psize = 10)
```



### 4.2.7 CT Dose reduction

#### 4.2.7.1 Forest plot

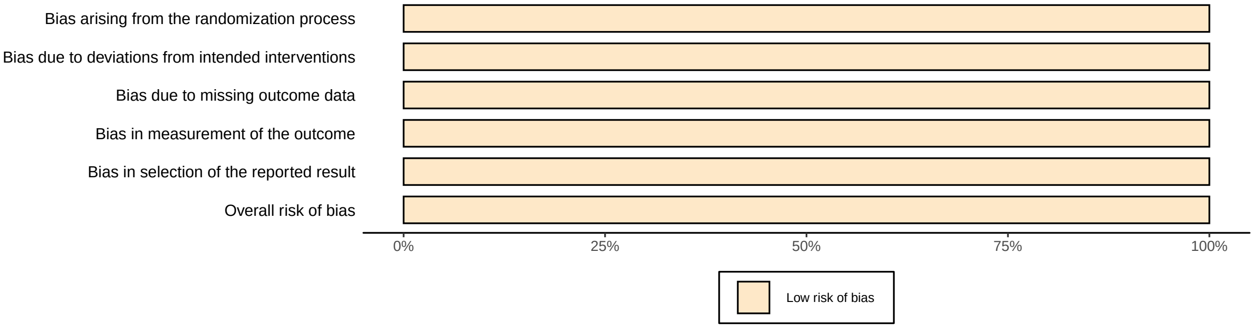
```
ct_dose <- metabin(
  HNC$event.e,
  HNC$n.e,
  HNC$event.c,
  HNC$n.c,
  sm = "RR",
  method = "MH",
  RR.cochrane = TRUE,
  MH.exact = TRUE,
  #allstudies = TRUE,
  HNC$studlab,
  subset = HNC$outclab == "CT_Dose" & HNC$C == 1,
  byvar = HNC$bias,
  comb.fixed = FALSE,
  comb.random = TRUE,
)

ct_dose_d <- data.frame(ct_dose)
rob_ct_dose_1 <- merge(rob_ct_dose_1, ct_dose_d[,c("w.random", "studlab")], by = "studlab", all = TRUE)

forest(ct_dose,
       xlab="CT Dose reduction",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 2,
       digits.se = 1,
       comb.fixed = FALSE,
       pooled.events = TRUE,
       #overall = FALSE,
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = TRUE,
       xlim = c(0.2, 5),
       #xlim    = "s",
       #plotwidth = "2cm",
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = C1,
       label.left = I1,
       fs.axis = 10,
       fs.lr = 10
)
```



### 4.2.7.2 Proportion of information at each level of risk of bias

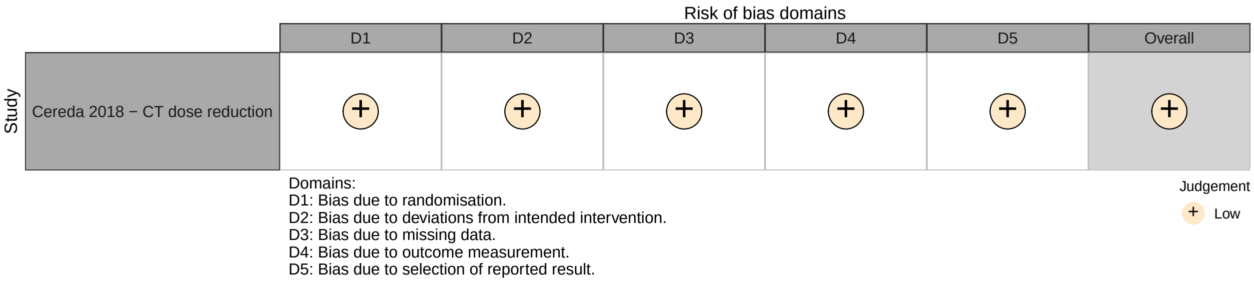
Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)

```
rob_summary(rob_ct_dose_1, tool = "ROB2", weighted = TRUE, overall = TRUE, colour = "colourblind")
```



### 4.2.7.3 Risk of bias assessments by study

```
rob_traffic_light(rob_ct_dose_1, tool = "ROB2", colour = "colourblind", psize = 10)
```

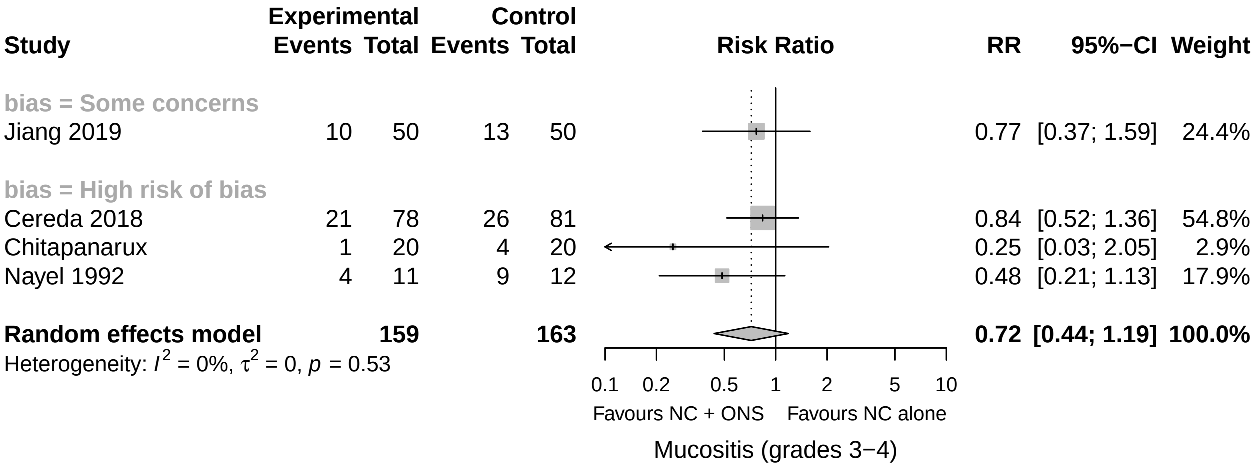


## 4.2.8 Mucositis (severe)

### 4.2.8.1 Forest plot

```
muco_1 <- metabin(
  HNC$event.e,
  HNC$n.e,
  HNC$event.c,
  HNC$n.c,
  sm = "RR",
  method = "MH",
  RR.cochrane = TRUE,
```

```
  MH.exact = FALSE,
  #allstudies = TRUE,
  HNC$studlab,
  subset = HNC$outclab == "Mucositis" & HNC$C == 1,
  byvar = HNC$bias,
  comb.fixed = FALSE,
  comb.random = TRUE
)

muco_1_d <- data.frame(muco_1)
rob_muco_1 <- merge(rob_muco_1, muco_1_d[,c("w.random", "studlab")], by = "studlab", all = TRUE)

forest(muco_1,
       xlab="Mucositis (grades 3-4)",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 2,
       digits.se = 1,
       comb.fixed = FALSE,
       #overall = FALSE,
       subgroup = FALSE,
       xlim = c(0.1, 10),
       #xlim     = "s",
       #plotwidth = "2cm",
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = C1,
       label.left = I1,
       fs.axis = 10,
       fs.lr = 10,
       hetstat = FALSE,
       overall.hetstat = TRUE
)
```

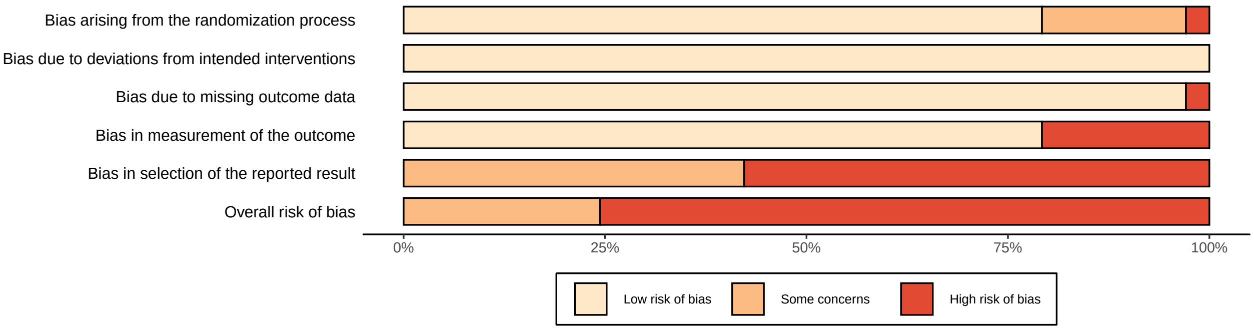


#### 4.2.8.2 Proportion of information at each level of risk of bias

Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result

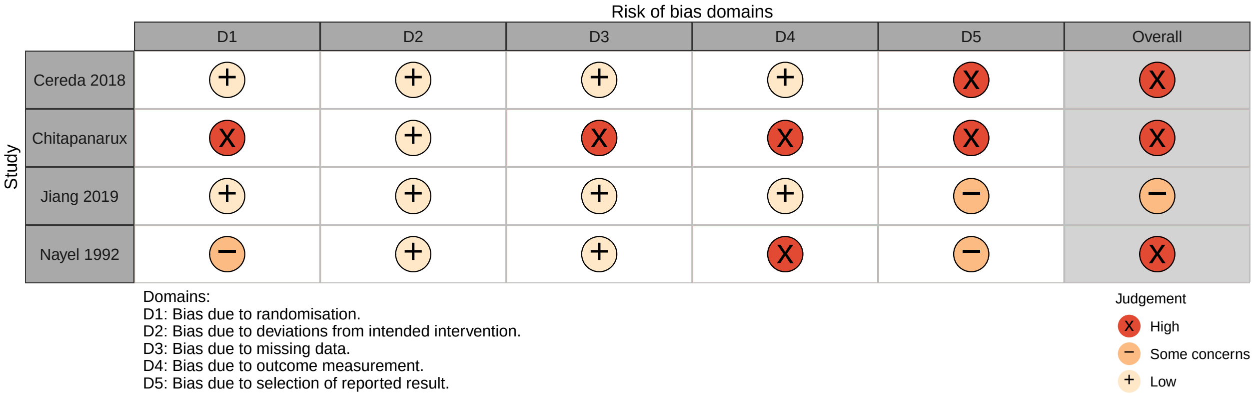
(when applicable)

```
rob_summary(rob_muco_1, tool = "ROB2", weighted = TRUE, overall = TRUE, colour = "colourblind")
```



#### 4.2.8.3 Risk of bias assessments by study

```
rob_traffic_light(rob_muco_1, tool = "ROB2", colour = "colourblind", psize = 10)
```


Risk of bias domains

| Study | D1 | D2 | D3 | D4 | D5 | Overall |
|---|---|---|---|---|---|---|
| Cereda 2018 | + | + | + | + | X | X |
| Chitapanarux | X | + | X | X | X | X |
| Jiang 2019 | + | + | + | + | − | − |
| Nayel 1992 | − | + | + | X | − | X |

Domains:
D1: Bias due to randomisation.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing data.
D4: Bias due to outcome measurement.
D5: Bias due to selection of reported result.

Judgement
X High
− Some concerns
+ Low

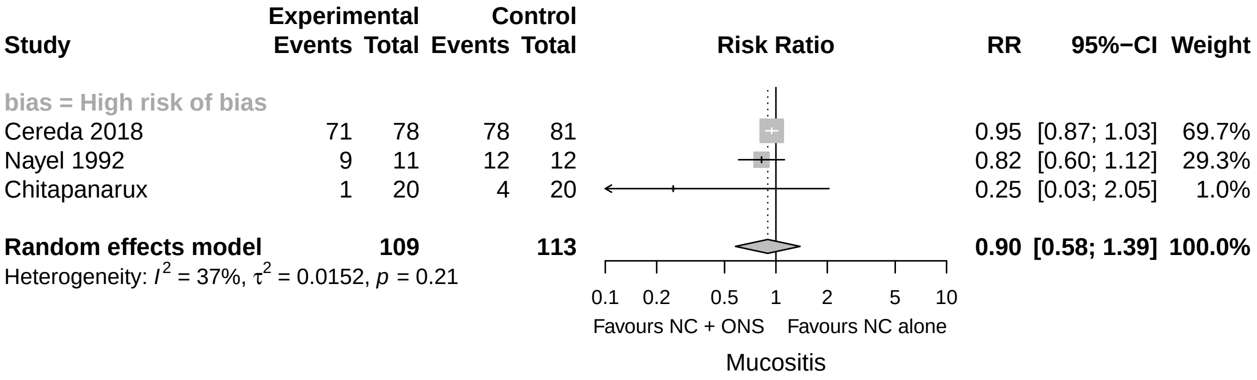
```
#orest(metainf(muco_1,
#               pooled = "random"))
```

### 4.2.9 Mucositis (overall)

#### 4.2.9.1 Forest plot

```
muco_g_1 <- metabin(
  HNC$event.e,
  HNC$n.e,
  HNC$event.c,
  HNC$n.c,
  sm = "RR",
  method = "MH",
  RR.cochrane = TRUE,
  MH.exact = FALSE,
  #allstudies = TRUE,
  HNC$studlab,
  subset = HNC$outclab == "Mucositis_g" & HNC$C == 1,
  byvar = HNC$bias,
```

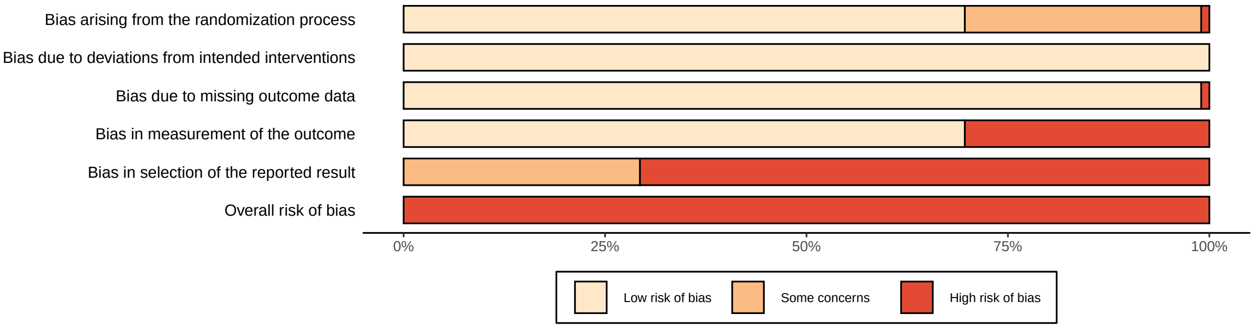
```
  comb.fixed = FALSE,
  comb.random = TRUE
)

muco_g_1_d <- data.frame(muco_g_1)
rob_muco_g_1 <- merge(rob_muco_g_1, muco_g_1_d[,c("w.random", "studlab")], by = "studlab", all = TRUE)

forest(muco_g_1,
       xlab="Mucositis",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 2,
       digits.se = 1,
       comb.fixed = FALSE,
       #overall = FALSE,
       subgroup = FALSE,
       xlim = c(0.1, 10),
       #xlim    = "s",
       #plotwidth = "2cm",
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = C1,
       label.left = I1,
       fs.axis = 10,
       fs.lr = 10,
       hetstat = FALSE,
       overall.hetstat = TRUE
)
```



#### 4.2.9.2 Proportion of information at each level of risk of bias

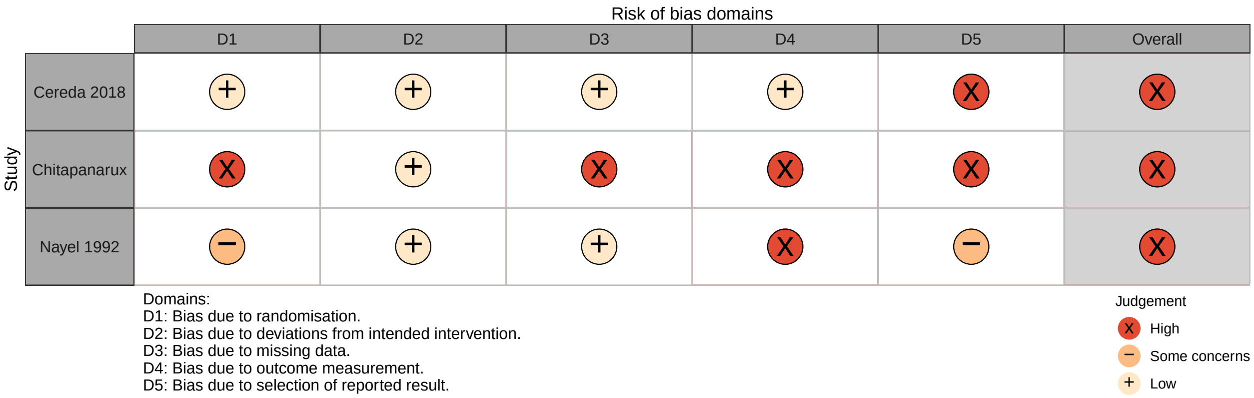
Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)

```
rob_summary(rob_muco_g_1, tool = "ROB2", weighted = TRUE, overall = TRUE, colour = "colourblind")
```



### 4.2.9.3 Risk of bias assessments by study

```
rob_traffic_light(rob_muco_g_1, tool = "ROB2", colour = "colourblind", psize = 10)
```



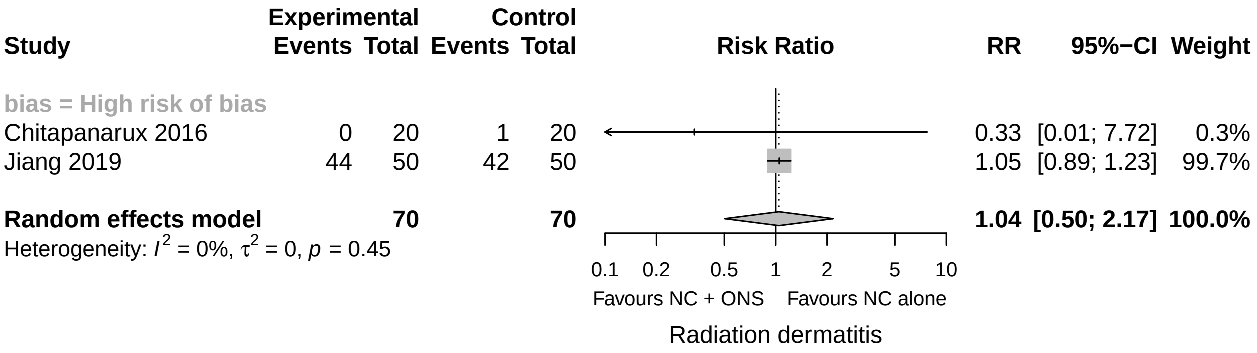
```
#forest(metainf(muco_g_1,
#                pooled = "random"))
```

## 4.2.10 Radiation dermatitis

### 4.2.10.1 Forest plot

```
derma_1 <- metabin(
  HNC$event.e,
  HNC$n.e,
  HNC$event.c,
  HNC$n.c,
  sm = "RR",
  method = "MH",
  RR.cochrane = TRUE,
  MH.exact = FALSE,
  #allstudies = TRUE,
  HNC$studlab,
  subset = HNC$outclab == "Derma" & HNC$C == 1,
  byvar = HNC$bias,
  comb.fixed = FALSE,
  comb.random = TRUE,
)
```

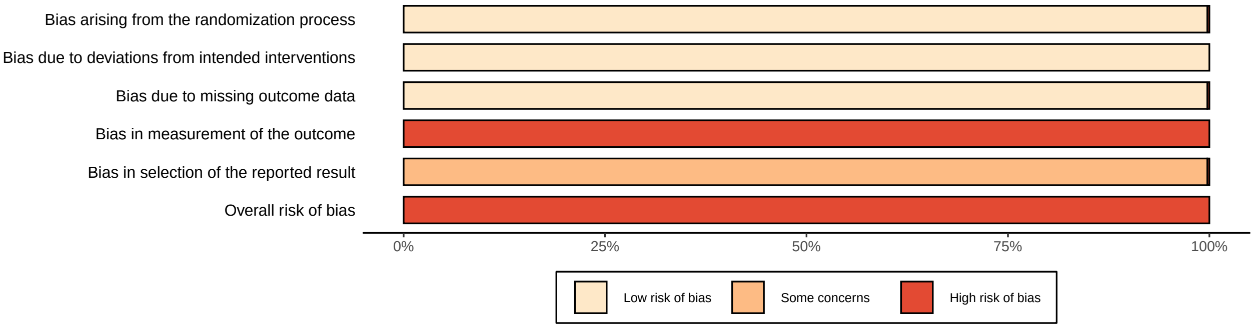
```r
derma_1_d <- data.frame(derma_1)
rob_derma_1 <- merge(rob_derma_1, derma_1_d[,c("w.random", "studlab")], by = "studlab", all = TRUE)

forest(derma_1,
       xlab="Radiation dermatitis",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 2,
       digits.se = 1,
       comb.fixed = FALSE,
       #overall = FALSE,
       subgroup = FALSE,
       xlim = c(0.1, 10),
       #xlim    = "s",
       #plotwidth = "2cm",
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = C1,
       label.left = I1,
       fs.axis = 10,
       fs.lr = 10,
       hetstat = FALSE,
       overall.hetstat = TRUE
)
```



### 4.2.10.2 Proportion of information at each level of risk of bias

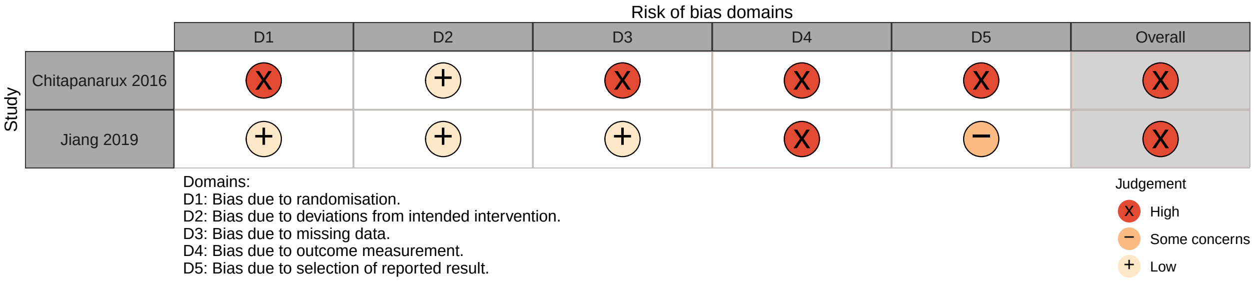
Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)

```r
rob_summary(rob_derma_1, tool = "ROB2", weighted = TRUE, overall = TRUE, colour = "colourblind")
```



### 4.2.10.3 Risk of bias assessments by study

```
rob_traffic_light(rob_derma_1, tool = "ROB2", colour = "colourblind", psize = 10)
```

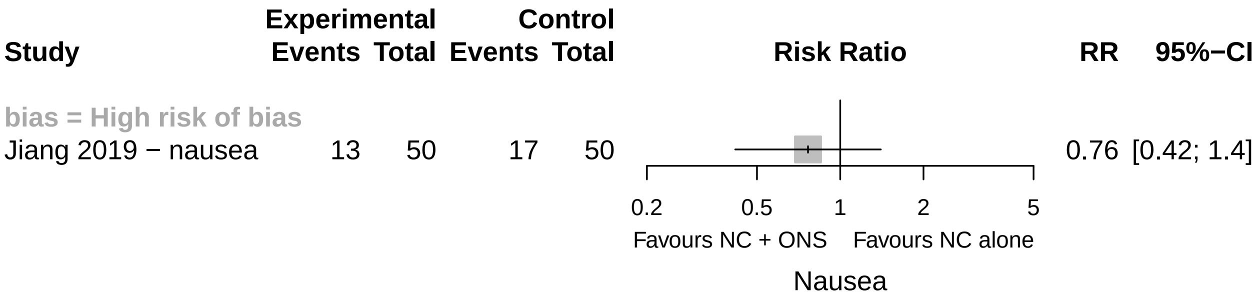


## 4.2.11 Nausea

### 4.2.11.1 Forest plot

```
nausea_1 <- metabin(
  HNC$event.e,
  HNC$n.e,
  HNC$event.c,
  HNC$n.c,
  sm = "RR",
  method = "MH",
  RR.cochrane = TRUE,
  MH.exact = FALSE,
  #allstudies = TRUE,
  HNC$studlab,
  subset = HNC$outclab == "Nausea" & HNC$C == 1,
  byvar = HNC$bias,
  comb.fixed = FALSE,
  comb.random = TRUE,
)

nausea_1_d <- data.frame(nausea_1)
rob_nausea_1 <- merge(rob_nausea_1, nausea_1_d[,c("w.random", "studlab")], by = "studlab", all = TRUE)

forest(nausea_1,
       xlab="Nausea",
       #ref = 10,
       #layout = "Revman5",
```

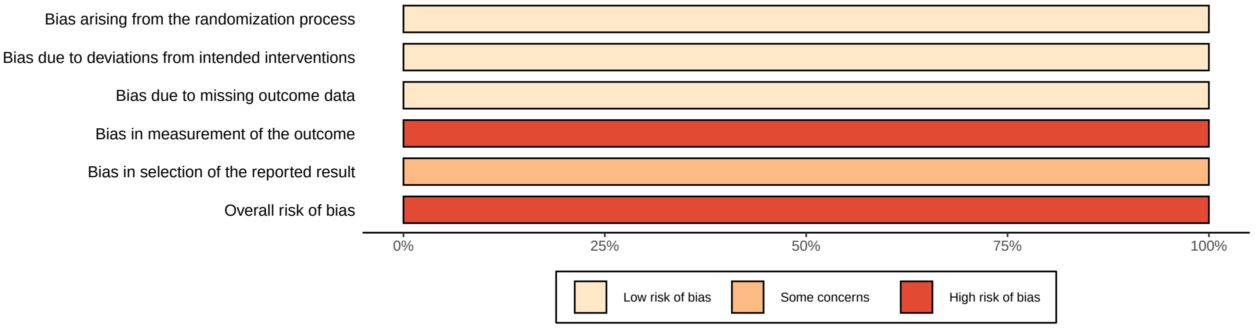
```
        layout = "meta",
        digits = 2,
        digits.se = 1,
        comb.fixed = FALSE,
        #overall = FALSE,
        subgroup = FALSE,
        xlim = c(0.2, 5),
        #xlim     = "s",
        #plotwidth = "2cm",
        colgap.forest = "0.5 cm",
        just = "right",
        label.right = C1,
        label.left = I1,
        fs.axis = 10,
        fs.lr = 10,
        hetstat = FALSE,
        overall.hetstat = TRUE
)
```



#### 4.2.11.2 Proportion of information at each level of risk of bias

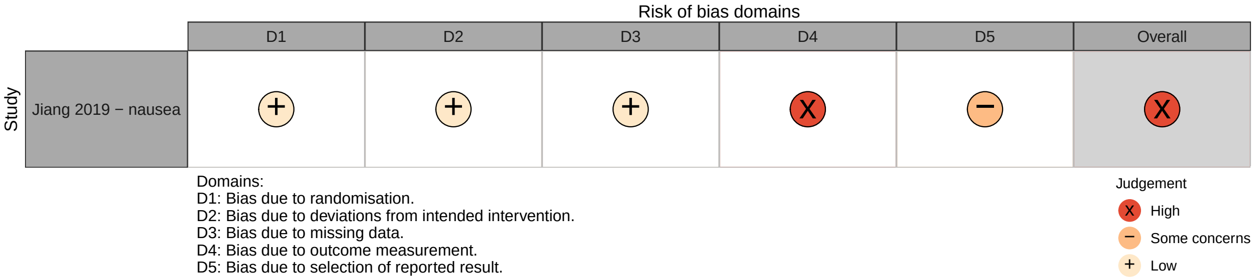
Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)

```
rob_summary(rob_nausea_1, tool = "ROB2", weighted = TRUE, overall = TRUE, colour = "colourblind")
```



#### 4.2.11.3 Risk of bias assessments by study

```
rob_traffic_light(rob_nausea_1, tool = "ROB2", colour = "colourblind", psize = 10)
```

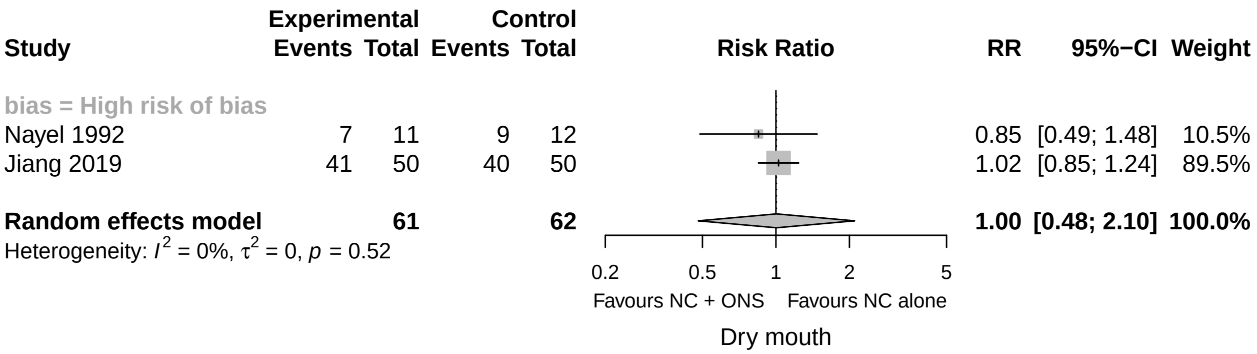


### 4.2.12 Dry mouth

#### 4.2.12.1 Forest plot

```
mouth_dry_1 <- metabin(
  HNC$event.e,
  HNC$n.e,
  HNC$event.c,
  HNC$n.c,
  sm = "RR",
  method = "MH",
  RR.cochrane = TRUE,
  MH.exact = FALSE,
  #allstudies = TRUE,
  HNC$studlab,
  subset = HNC$outclab == "Mouth_dry" & HNC$C == 1,
  byvar = HNC$bias,
  comb.fixed = FALSE,
  comb.random = TRUE
)

mouth_dry_1_d <- data.frame(mouth_dry_1)
rob_mouth_dry_1 <- merge(rob_mouth_dry_1, mouth_dry_1_d[,c("w.random", "studlab")], by = "studlab", all

forest(mouth_dry_1,
       xlab="Dry mouth",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 2,
       digits.se = 1,
       comb.fixed = FALSE,
       #overall = FALSE,
       subgroup = FALSE,
       xlim = c(0.2, 5),
       #xlim    = "s",
       #plotwidth = "2cm",
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = C1,
       label.left = I1,
       fs.axis = 10,
       fs.lr = 10,
```

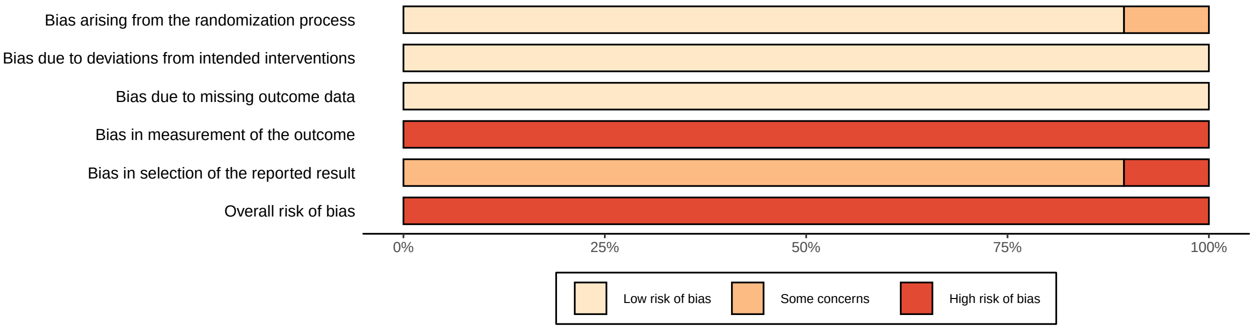
```
        hetstat = FALSE,
        overall.hetstat = TRUE
)
```



#### 4.2.12.2 Proportion of information at each level of risk of bias

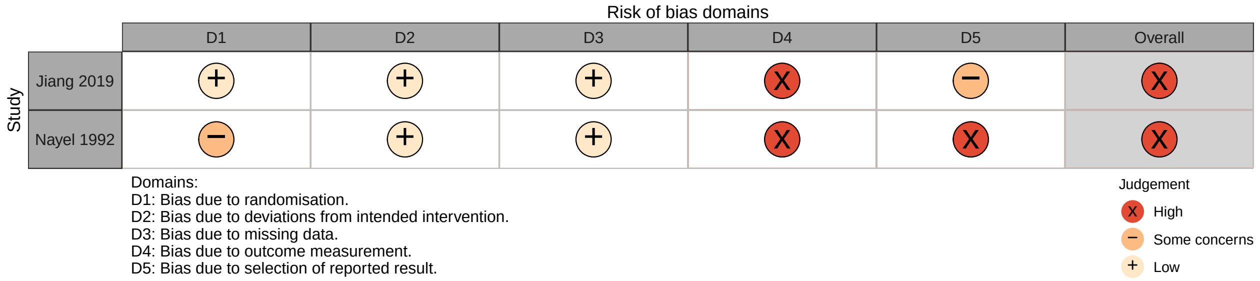
Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)

```
rob_summary(rob_mouth_dry_1, tool = "ROB2", weighted = TRUE, overall = TRUE, colour = "colourblind")
```



#### 4.2.12.3 Risk of bias assessments by study

```
rob_traffic_light(rob_mouth_dry_1, tool = "ROB2", colour = "colourblind", psize = 10)
```



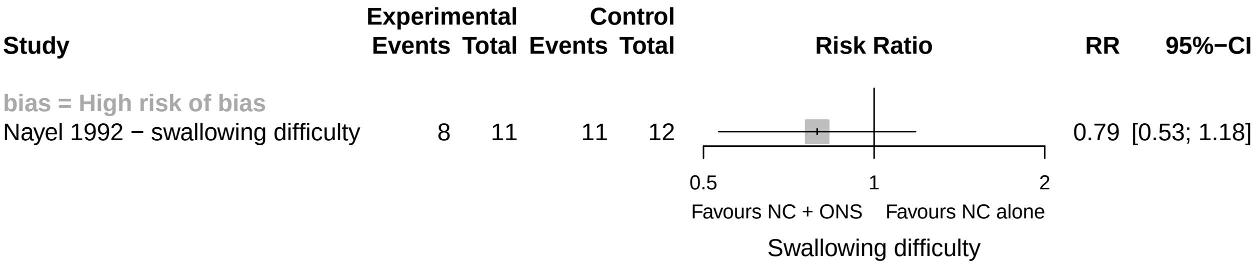
| Study | D1 | D2 | D3 | D4 | D5 | Overall |
|---|---|---|---|---|---|---|
| Jiang 2019 | + | + | + | X | − | X |
| Nayel 1992 | − | + | + | X | X | X |

Domains:
D1: Bias due to randomisation.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing data.
D4: Bias due to outcome measurement.
D5: Bias due to selection of reported result.

### 4.2.13 Swallowing difficulty

#### 4.2.13.1 Forest plot

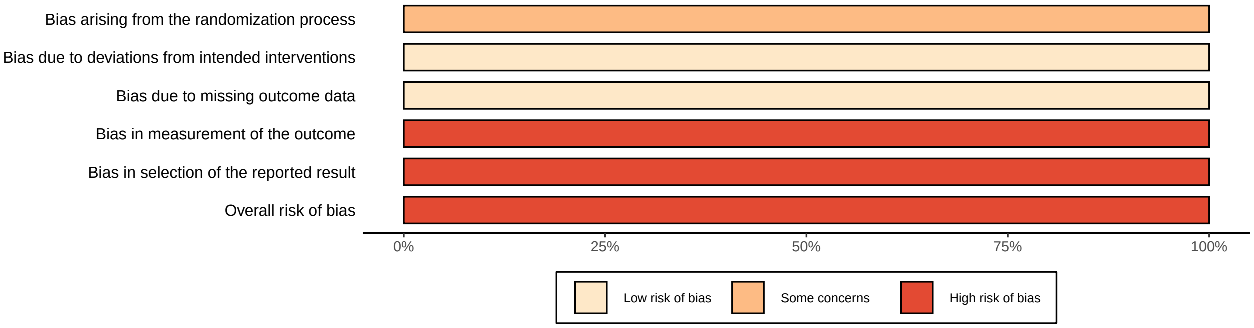
```
swallow_1 <- metabin(
  HNC$event.e,
  HNC$n.e,
  HNC$event.c,
  HNC$n.c,
  sm = "RR",
  method = "MH",
  RR.cochrane = TRUE,
  MH.exact = FALSE,
  #allstudies = TRUE,
  HNC$studlab,
  subset = HNC$outclab == "Swallow" & HNC$C == 1,
  byvar = HNC$bias,
  comb.fixed = FALSE,
  comb.random = TRUE,
)

swallow_1_d <- data.frame(swallow_1)
rob_swallow_1 <- merge(rob_swallow_1, swallow_1_d[,c("w.random", "studlab")], by = "studlab", all = TRU

forest(swallow_1,
       xlab="Swallowing difficulty",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 2,
       digits.se = 1,
       comb.fixed = FALSE,
       #overall = FALSE,
       subgroup = FALSE,
       xlim = c(0.5, 2),
       #xlim    = "s",
       #plotwidth = "2cm",
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = C1,
       label.left = I1,
       fs.axis = 10,
       fs.lr = 10,
       hetstat = FALSE,
       overall.hetstat = TRUE
)
```



#### 4.2.13.2 Proportion of information at each level of risk of bias

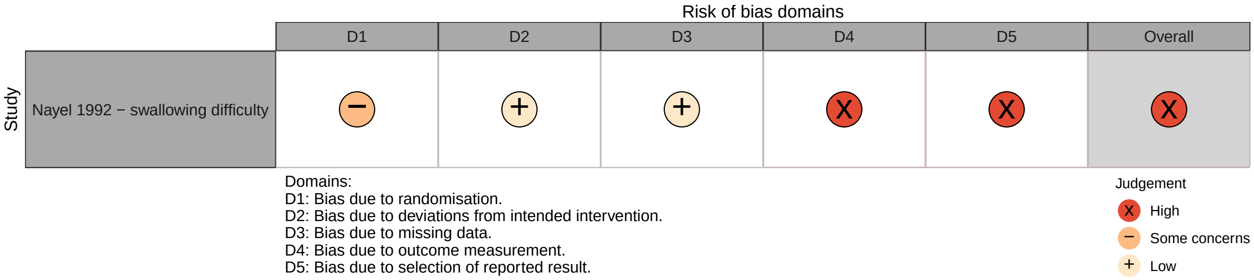
Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)

```
rob_summary(rob_swallow_1, tool = "ROB2", weighted = TRUE, overall = TRUE, colour = "colourblind")
```



#### 4.2.13.3 Risk of bias assessments by study

```
rob_traffic_light(rob_swallow_1, tool = "ROB2", colour = "colourblind", psize = 10)
```

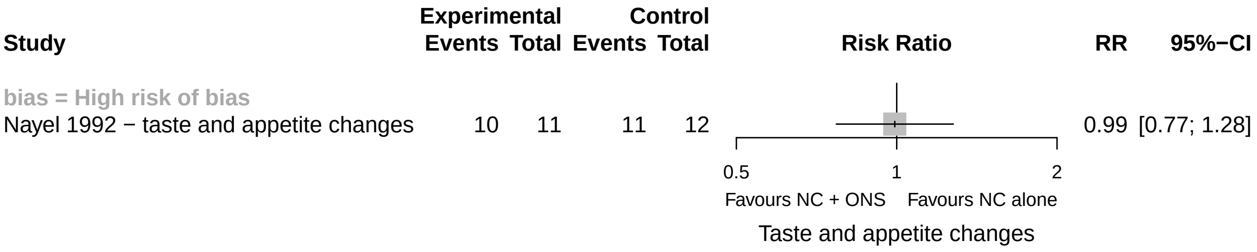


### 4.2.14 Taste and appetite changes

#### 4.2.14.1 Forest plot

```
taste_app_1 <- metabin(
  HNC$event.e,
  HNC$n.e,
  HNC$event.c,
  HNC$n.c,
  sm = "RR",
  method = "MH",
  RR.cochrane = TRUE,
  MH.exact = FALSE,
  #allstudies = TRUE,
  HNC$studlab,
  subset = HNC$outclab == "Taste_App" & HNC$C == 1,
  byvar = HNC$bias,
  comb.fixed = FALSE,
  comb.random = TRUE,
)
```

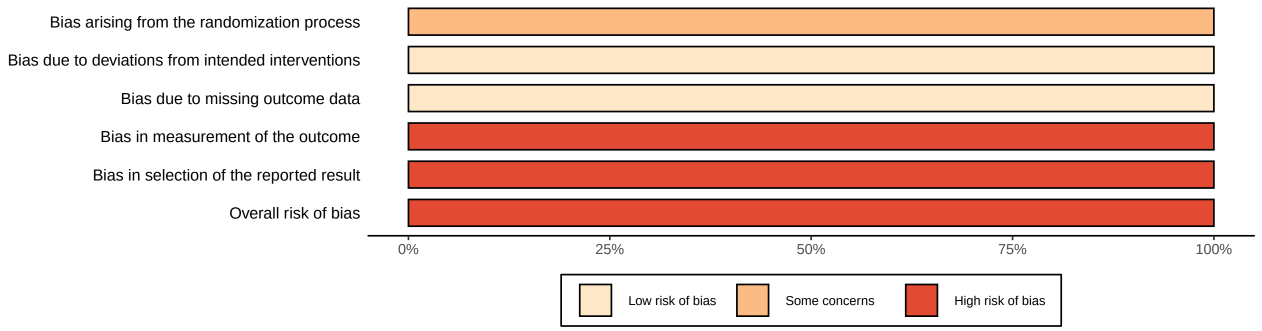
```
taste_app_1_d <- data.frame(taste_app_1)
rob_taste_app_1 <- merge(rob_taste_app_1, taste_app_1_d[,c("w.random", "studlab")], by = "studlab", all

forest(taste_app_1,
       xlab="Taste and appetite changes",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 2,
       digits.se = 1,
       comb.fixed = FALSE,
       #overall = FALSE,
       subgroup = FALSE,
       xlim = c(0.5, 2),
       #xlim    = "s",
       #plotwidth = "2cm",
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = C1,
       label.left = I1,
       fs.axis = 10,
       fs.lr = 10,
       hetstat = FALSE,
       overall.hetstat = TRUE
)
```



### 4.2.14.2 Proportion of information at each level of risk of bias

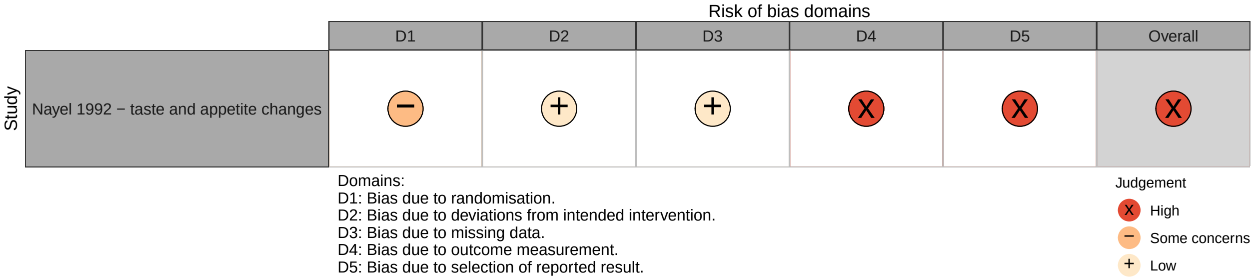
Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)

```
rob_summary(rob_taste_app_1, tool = "ROB2", weighted = TRUE, overall = TRUE, colour = "colourblind")
```



#### 4.2.14.3 Risk of bias assessments by study

```
rob_traffic_light(rob_taste_app_1, tool = "ROB2", colour = "colourblind", psize = 10)
```

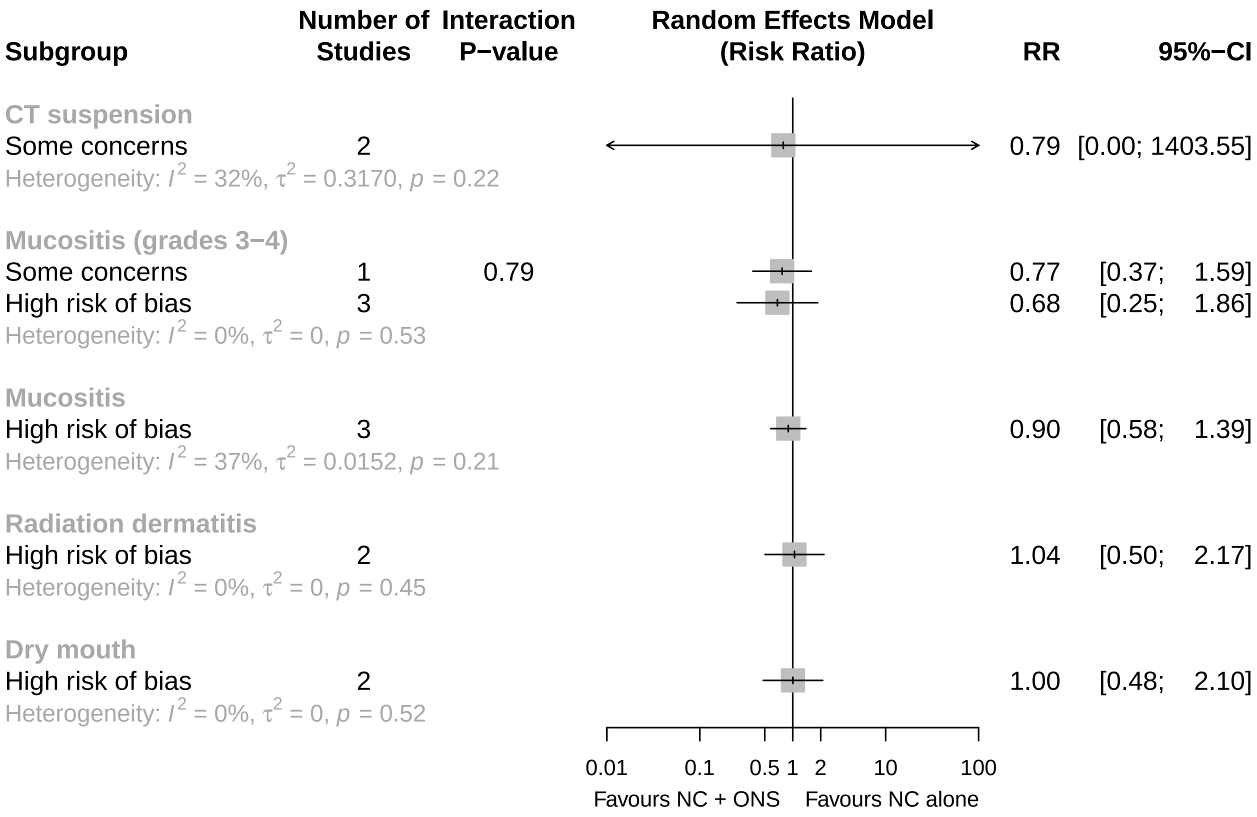


### 4.2.15 Summary of treatment tolerance outcomes

#### 4.2.15.1 Results of meta-analysis

```
tol_1_b <- metabind(#rt_susp,
                    ct_susp,
                    #rt_int5,
                    #ccrt_inc,
                    #rt_dose,
                    #ct_dose,
                    muco_1,
                    muco_g_1,
                    derma_1,
                    #nausea_1,
                    mouth_dry_1,
                    #swallow_1,
                    #taste_app_1,
                    name = c(#"RT suspension",
                             "CT suspension",
                             #"RT interruption >= 5 days",
                             #"Incomplete CCRT",
                             #"RT dose reduction",
                             #"CT dose reduction",
                             "Mucositis (grades 3-4)",
                             "Mucositis",
                             "Radiation dermatitis",
                             #"Nausea",
                             "Dry mouth"
                             #"Swallowing difficulties",
                             #"Taste and appetite changes"
                             ),
                    pooled = "random")

forest(tol_1_b,
       #layout = "meta",
       #leftcols = c("Subgroup"),
       digits = 2,
       digits.se = 1,
       subgroup = FALSE,
```

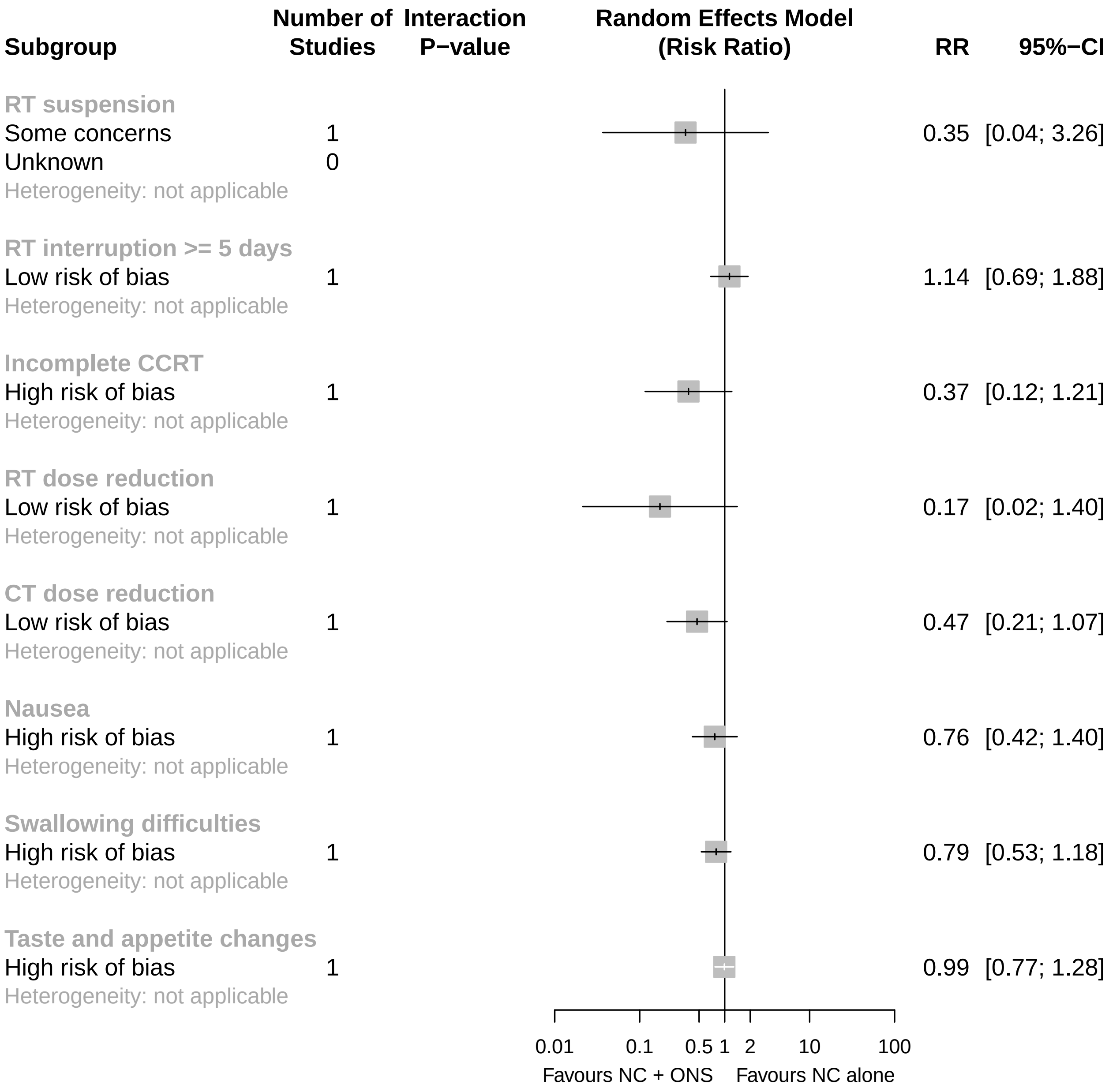
```
       xlim = c(0.01, 100),
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = C1,
       label.left = I1,
       fs.axis = 10,
       fs.lr = 10,
       hetstat = TRUE,
       overall.hetstat = FALSE,
       digits.addcols.left = 0,
       test.effect.subgroup.random = FALSE,
       test.subgroup = FALSE,
       test.overall = FALSE
)
```



#### 4.2.15.2 Results of structured reporting (no meta-analysis)

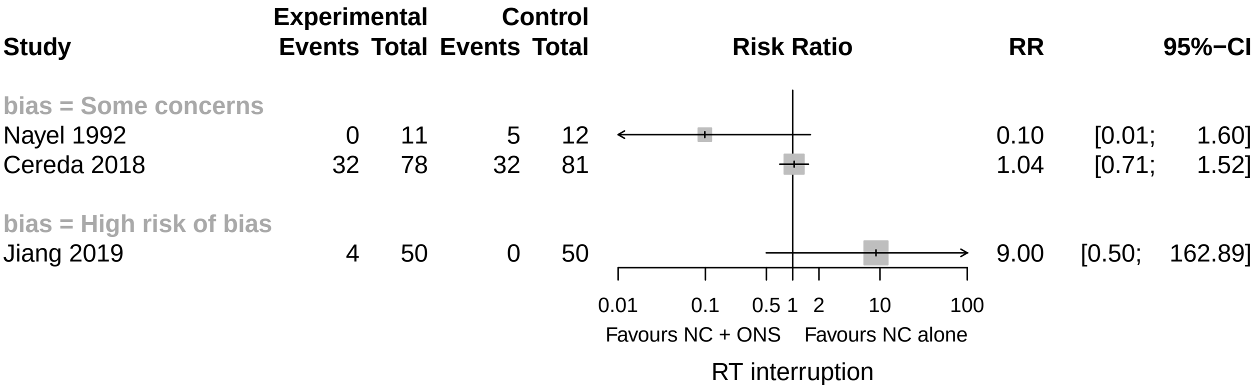
```
tol_1_c <- metabind(rt_susp,
                    rt_int5,
                    ccrt_inc,
                    rt_dose,
                    ct_dose,
                    nausea_1,
                    swallow_1,
                    taste_app_1,
                    name = c("RT suspension",
                             "RT interruption >= 5 days",
```

```
                             "Incomplete CCRT",
                             "RT dose reduction",
                             "CT dose reduction",
                             "Nausea",
                             "Swallowing difficulties",
                             "Taste and appetite changes"
                             ),
                    pooled = "random")

forest(tol_1_c,
       #layout = "meta",
       #leftcols = c("Subgroup"),
       digits = 2,
       digits.se = 1,
       subgroup = FALSE,
       xlim = c(0.01, 100),
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = C1,
       label.left = I1,
       fs.axis = 10,
       fs.lr = 10,
       hetstat = TRUE,
       overall.hetstat = FALSE,
       digits.addcols.left = 0,
       test.effect.subgroup.random = FALSE,
       test.subgroup = FALSE,
       test.overall = FALSE
)
```



```r
forest(rt_int,
       xlab="RT interruption",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 2,
       digits.se = 1,
       comb.fixed = FALSE,
       pooled.events = TRUE,
       #overall = FALSE,
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = FALSE,
       overall = FALSE,
       xlim = c(0.01, 100),
```

```
       #xlim    = "s",
       #plotwidth = "2cm",
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = C1,
       label.left = I1,
       fs.axis = 10,
       fs.lr = 10
)
```



| Study | Experimental Events | Experimental Total | Control Events | Control Total | RR | 95%−CI |
|---|---|---|---|---|---|---|
| bias = Some concerns | | | | | | |
| Nayel 1992 | 0 | 11 | 5 | 12 | 0.10 | [0.01; 1.60] |
| Cereda 2018 | 32 | 78 | 32 | 81 | 1.04 | [0.71; 1.52] |
| bias = High risk of bias | | | | | | |
| Jiang 2019 | 4 | 50 | 0 | 50 | 9.00 | [0.50; 162.89] |

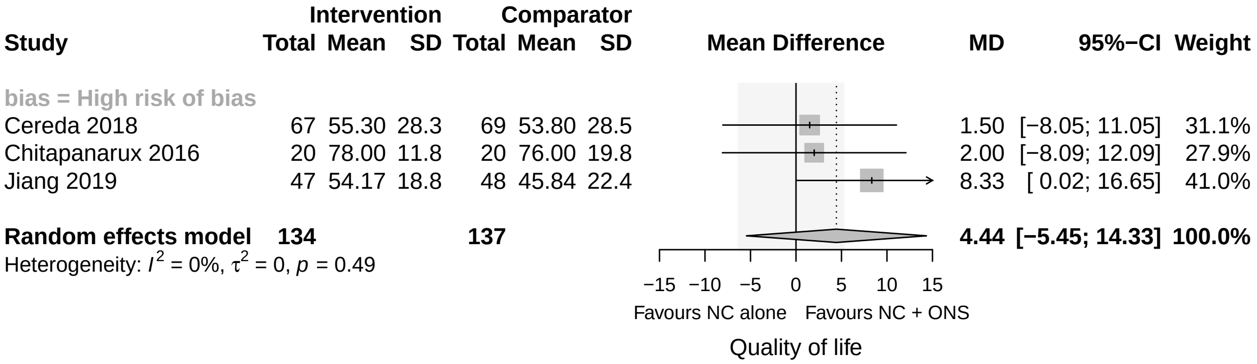
## 4.3 Quality of life (end of treatment)

### 4.3.1 Global quality of life

#### 4.3.1.1 Forest plot

```
QoL <- metacont(
  HNC$n.e,
  HNC$mean.e,
  HNC$sd.e,
  HNC$n.c,
  HNC$mean.c,
  HNC$sd.c,
  HNC$studlab,
  data = HNC,
  subset = HNC$outclab == "QoL" & HNC$C == 1,
  byvar = HNC$bias,
)

QoL_d <- data.frame(QoL)
rob_QoL_1_1 <- merge(rob_QoL_1_1, QoL_d[,c("w.random", "studlab")], by = "studlab", all = TRUE)
rob_QoL_1_1_S <- subset(rob_QoL_1_1,studlab != "Jiang 2019")

forest(QoL,
       xlab="Quality of life",
       layout = "meta",
       digits = 2,
       digits.se = 1,
       comb.fixed = FALSE,
       xlim = c(-15,15),
       plotwidth = "5cm",
```

```
        subgroup = FALSE,
        hetstat = FALSE,
        overall.hetstat = TRUE,
        colgap.forest = "0.5 cm",
        just = "right",
        label.right = I1,
        label.left = C1,
        fs.axis = 10,
        fs.lr = 10,
        lower.equi = -6.5, # Equivalence limits
        upper.equi = 5.4,
        lty.equi = 1,
        fill.equi = "#f5f5f5",
        col.equi = "white",
        lab.e = "Intervention",
        lab.c = "Comparator"
)
```



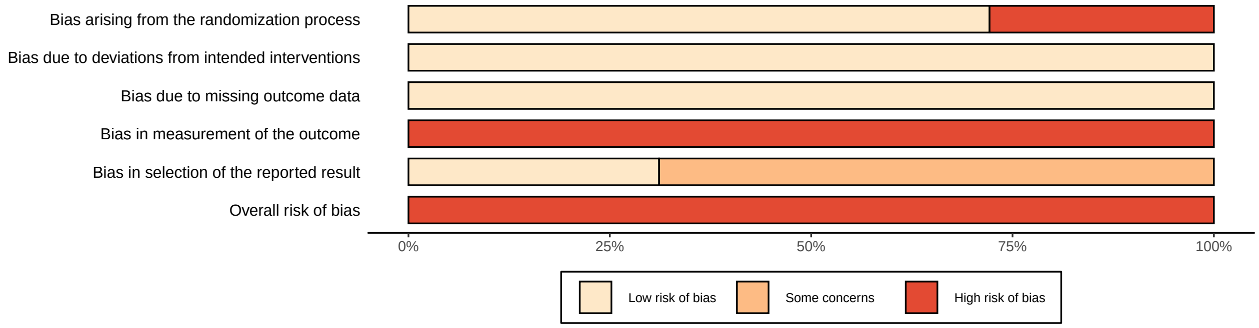
MIDs for the global health status (QL) scale for improvement (deterioration) were QL: 5.4 (- 6.5) and SF: 4.9 (- 7.7) in head and neck cancer patients (shaded area)

Musoro J, Coens C, Fiteni F, et al. Evidence-based approach to determine meaningful change in scores of the EORTC QLQ-C30 in breast and head and neck cancer: on behalf of the EORTC Breast, Head and Neck and Quality of Life Groups. 25th annual conference of the international society for quality of life research, Dublin, Ireland. Qual Life Res 2018;27 (Suppl 1): ab101.4, 18. https://doi.org/10.1007/s11136-018-1946-9

#### 4.3.1.2 Proportion of information at each level of risk of bias

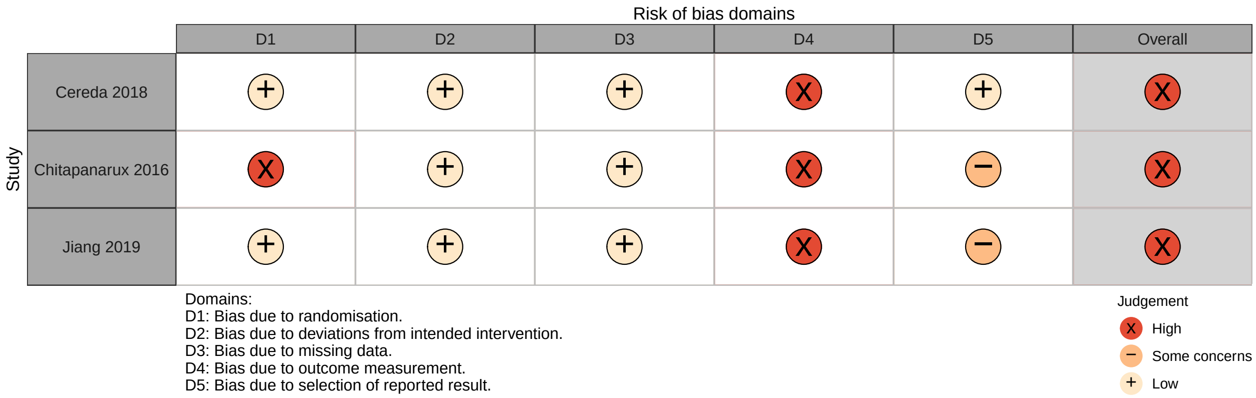
Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)

```
rob_summary(rob_QoL_1_1, tool = "ROB2", weighted = TRUE, overall = TRUE, colour = "colourblind")
```



#### 4.3.1.3 Risk of bias assessments by study

```r
rob_traffic_light(rob_QoL_1_1, tool = "ROB2", colour = "colourblind", psize = 10)
```



```r
#forest(metainf(QoL,
#                pooled = "random"))
```

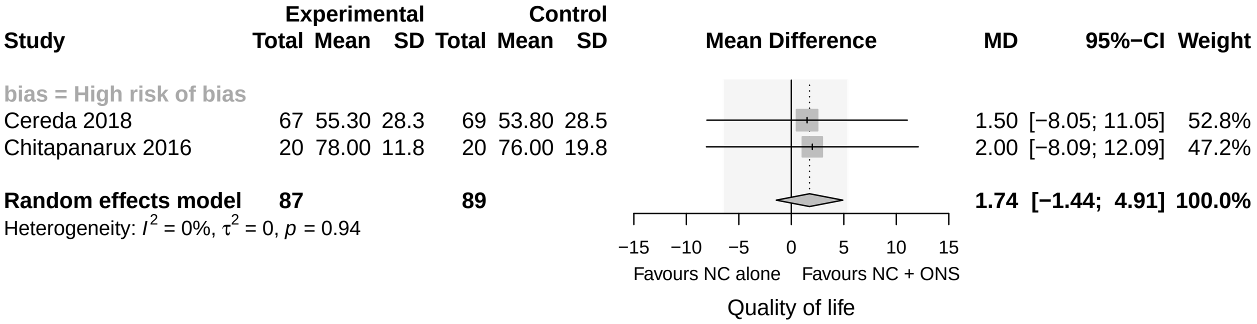
### 4.3.2 Sensitivity analysis

Excluding Jiang 2019, because mean and standard deviation for this study were inputted (as described in the methods section of the primary report).

#### 4.3.2.1 Forest plot

```r
QoL_S <- update.meta(QoL, subset = HNC$outclab == "QoL" & HNC$C == 1 & HNC$studlab != "Jiang 2019")

forest(QoL_S,
       xlab="Quality of life",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 2,
       digits.se = 1,
       comb.fixed = FALSE,
       xlim = c(-15,15),
       #plotwidth = "2cm",
       subgroup = FALSE,
       hetstat = FALSE,
```

```
        overall.hetstat = TRUE,
        #pooled.events = TRUE,
        #resid.hetstat = FALSE,
        colgap.forest = "0.5 cm",
        just = "right",
        label.right = I1,
        label.left = C1,
        fs.axis = 10,
        fs.lr = 10,
        lower.equi = -6.5, # Equivalence limits
        upper.equi = 5.4,
        lty.equi = 1,
        fill.equi = "#f5f5f5",
        col.equi = "white",
)
```



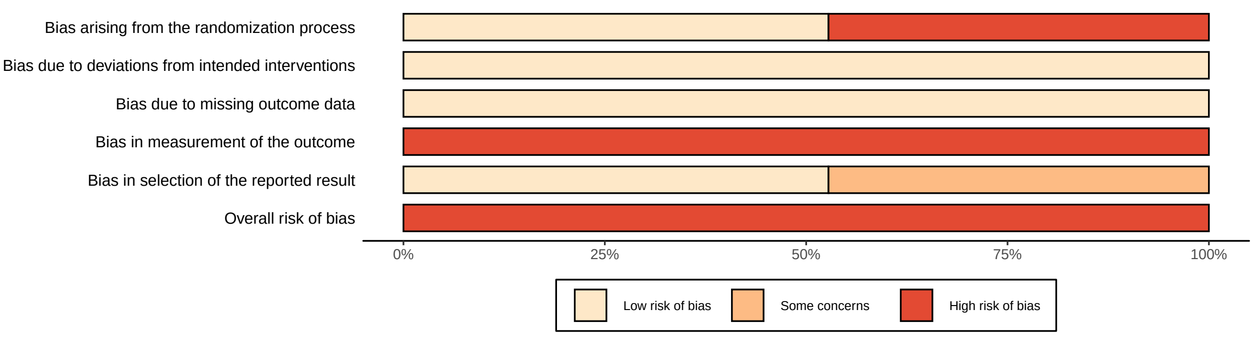
| Study | Experimental Total | Experimental Mean | Experimental SD | Control Total | Control Mean | Control SD | MD | 95%−CI | Weight |
|---|---|---|---|---|---|---|---|---|---|
| bias = High risk of bias | | | | | | | | | |
| Cereda 2018 | 67 | 55.30 | 28.3 | 69 | 53.80 | 28.5 | 1.50 | [−8.05; 11.05] | 52.8% |
| Chitapanarux 2016 | 20 | 78.00 | 11.8 | 20 | 76.00 | 19.8 | 2.00 | [−8.09; 12.09] | 47.2% |
| **Random effects model** | **87** | | | **89** | | | **1.74** | **[−1.44; 4.91]** | **100.0%** |

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.94$

### 4.3.2.2 Proportion of information at each level of risk of bias

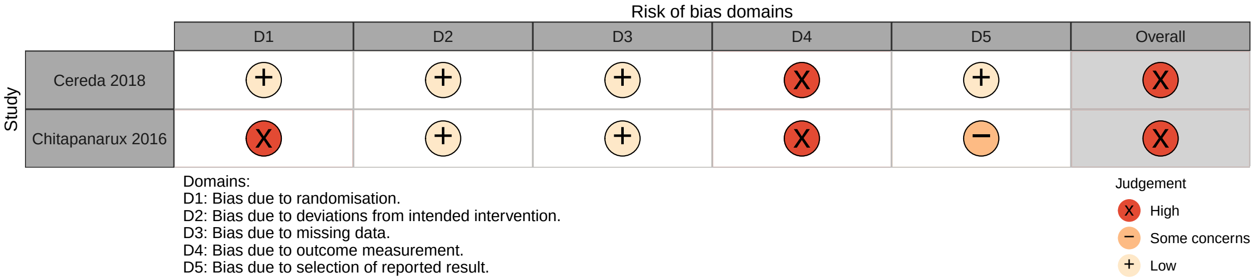
Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)

```
rob_summary(rob_QoL_1_1_S, tool = "ROB2", weighted = TRUE, overall = TRUE, colour = "colourblind")
```



### 4.3.2.3 Risk of bias assessments by study

```
rob_traffic_light(rob_QoL_1_1_S, tool = "ROB2", colour = "colourblind", psize = 10)
```



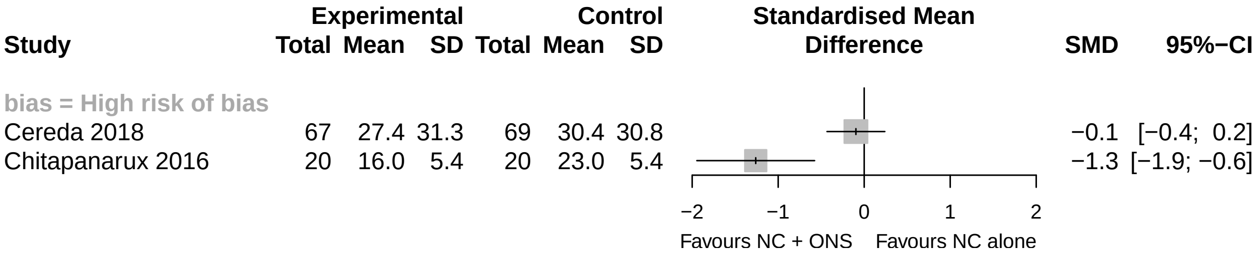
```
#forest(metainf(bw_1_1,
#               pooled = "random"))
```

### 4.3.3 Quality of life subscales

#### 4.3.3.1 Appetite loss

```
QoL_Appetite <- metacont(
  HNC$n.e,

  HNC$mean.e,

  HNC$sd.e,

  HNC$n.c,

  HNC$mean.c,

  HNC$sd.c,

  HNC$studlab,

  data = HNC,

  subset = HNC$outclab == "QoL_Appetite" & HNC$C == 1,

  byvar = HNC$bias,
  sm = "SMD",
)

forest(QoL_Appetite,
       xlab="QoL_Appetite",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 1,
       digits.se = 1,
       comb.fixed = FALSE,
       xlim = c(-2, 2),
       #plotwidth = "2cm",
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = FALSE,
```

```
       #pooled.events = TRUE,
       #resid.hetstat = FALSE,
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = C1,
       label.left = I1,
       fs.axis = 10,
       fs.lr = 10,
       overall = FALSE,
)
```

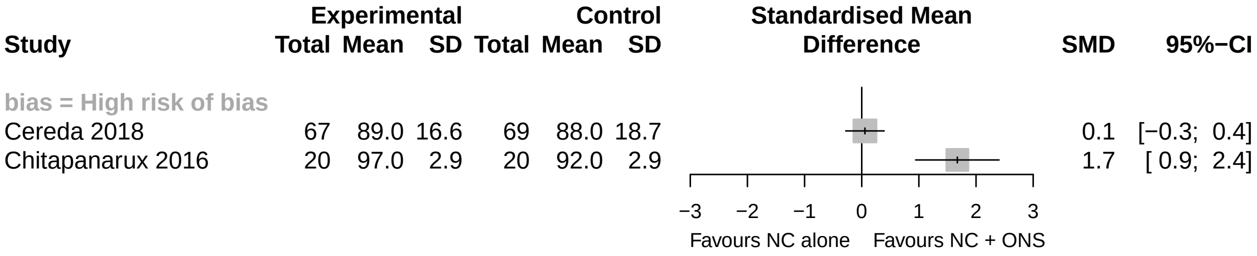


| Study | Experimental Total | Experimental Mean | Experimental SD | Control Total | Control Mean | Control SD | SMD | 95%−CI |
|---|---|---|---|---|---|---|---|---|
| bias = High risk of bias | | | | | | | | |
| Cereda 2018 | 67 | 27.4 | 31.3 | 69 | 30.4 | 30.8 | −0.1 | [−0.4; 0.2] |
| Chitapanarux 2016 | 20 | 16.0 | 5.4 | 20 | 23.0 | 5.4 | −1.3 | [−1.9; −0.6] |

#### 4.3.3.2 Cognitive

```
QoL_Cognitive <- metacont(
  HNC$n.e,

  HNC$mean.e,

  HNC$sd.e,

  HNC$n.c,

  HNC$mean.c,

  HNC$sd.c,

  HNC$studlab,

  data = HNC,

  subset = HNC$outclab == "QoL_Cognitive" & HNC$C == 1,

  byvar = HNC$bias,
  sm = "SMD",
)

forest(QoL_Cognitive,
       xlab="QoL_Cognitive",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 1,
       digits.se = 1,
       comb.fixed = FALSE,
```

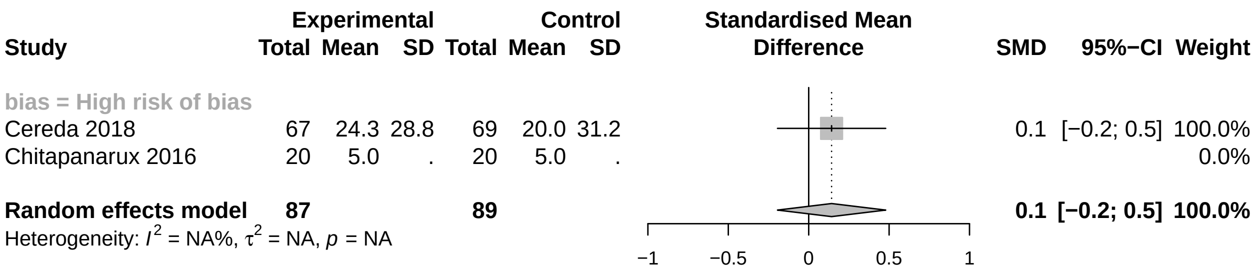
```
       #plotwidth = "2cm"
       xlim = c(-3, 3),
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = FALSE,
       #pooled.events = TRUE,
       #resid.hetstat = FALSE,
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = I1,
       label.left = C1,
       fs.axis = 10,
       fs.lr = 10,
       overall = FALSE
)
```



### 4.3.3.3 Constipation

```
QoL_Constipation <- metacont(
  HNC$n.e,

  HNC$mean.e,

  HNC$sd.e,

  HNC$n.c,

  HNC$mean.c,

  HNC$sd.c,

  HNC$studlab,

  data = HNC,

  subset = HNC$outclab == "QoL_Constipation" & HNC$C == 1,

  byvar = HNC$bias,
  sm = "SMD",
)

forest(QoL_Constipation,
       xlab="QoL_Constipation",
       #ref = 10,
       #layout = "Revman5",
```

```
       layout = "meta",
       digits = 1,
       digits.se = 1,
       comb.fixed = FALSE,
       #plotwidth = "2cm",
       xlim = c(-1, 1),
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = TRUE,
       #pooled.events = TRUE,
       #resid.hetstat = FALSE,
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = C1,
       label.left = I1,
       fs.axis = 10,
       fs.lr = 10
)
```



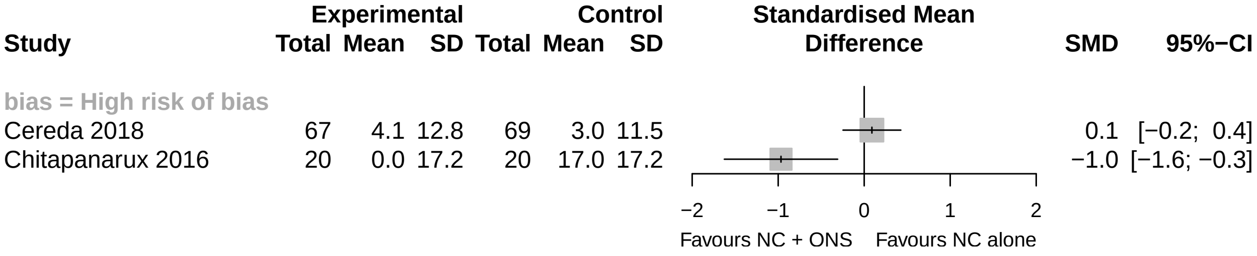
| | Experimental | | | Control | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Study** | **Total** | **Mean** | **SD** | **Total** | **Mean** | **SD** | **SMD** | **95%−CI** | **Weight** |
| bias = High risk of bias | | | | | | | | | |
| Cereda 2018 | 67 | 24.3 | 28.8 | 69 | 20.0 | 31.2 | 0.1 | [−0.2; 0.5] | 100.0% |
| Chitapanarux 2016 | 20 | 5.0 | . | 20 | 5.0 | . | | | 0.0% |
| **Random effects model** | **87** | | | **89** | | | **0.1** | **[−0.2; 0.5]** | **100.0%** |

Heterogeneity: $I^2$ = NA%, $\tau^2$ = NA, $p$ = NA

#### 4.3.3.4 Diarrhoea

```
QoL_Diarrhoea <- metacont(
  HNC$n.e,

  HNC$mean.e,

  HNC$sd.e,

  HNC$n.c,

  HNC$mean.c,

  HNC$sd.c,

  HNC$studlab,

  data = HNC,

  subset = HNC$outclab == "QoL_Diarrhoea" & HNC$C == 1,

  byvar = HNC$bias,
  sm = "SMD",
)

forest(QoL_Diarrhoea,
```

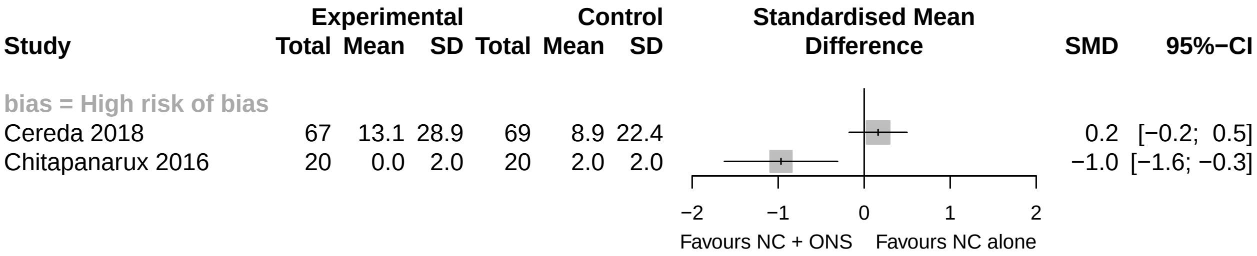
```
       xlab="QoL_Diarrhoea",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 1,
       digits.se = 1,
       comb.fixed = FALSE,
       #plotwidth = "2cm",
       xlim = c(-2, 2),
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = FALSE,
       #pooled.events = TRUE,
       #resid.hetstat = FALSE,
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = C1,
       label.left = I1,
       fs.axis = 10,
       fs.lr = 10,
       overall = FALSE
)
```



#### 4.3.3.5 Dyspnoea

```
QoL_Dyspnoea <- metacont(
  HNC$n.e,

  HNC$mean.e,

  HNC$sd.e,

  HNC$n.c,

  HNC$mean.c,

  HNC$sd.c,

  HNC$studlab,

  data = HNC,

  subset = HNC$outclab == "QoL_Dyspnoea" & HNC$C == 1,
```

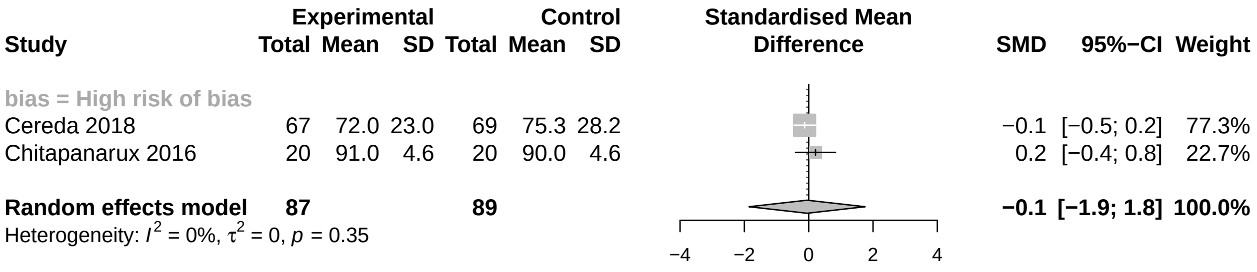
```
  byvar = HNC$bias,
  sm = "SMD",
)

forest(QoL_Dyspnoea,
       xlab="QoL_Dyspnoea",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 1,
       digits.se = 1,
       comb.fixed = FALSE,
       #plotwidth = "2cm"
       xlim = c(-2, 2),
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = FALSE,
       #pooled.events = TRUE,
       #resid.hetstat = FALSE,
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = C1,
       label.left = I1,
       fs.axis = 10,
       fs.lr = 10,
       overall = FALSE
)
```



#### 4.3.3.6 Emotional

```
QoL_Emotional <- metacont(
  HNC$n.e,

  HNC$mean.e,

  HNC$sd.e,

  HNC$n.c,

  HNC$mean.c,

  HNC$sd.c,

  HNC$studlab,
```

```
  data = HNC,

  subset = HNC$outclab == "QoL_Emotional" & HNC$C == 1,

  byvar = HNC$bias,
  sm = "SMD",
)

forest(QoL_Emotional,
       xlab="QoL_Emotional",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 1,
       digits.se = 1,
       comb.fixed = FALSE,
       #plotwidth = "2cm"
       xlim = c(-5, 5),
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = TRUE,
       #pooled.events = TRUE,
       #resid.hetstat = FALSE,
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = I1,
       label.left = C1,
       fs.axis = 10,
       fs.lr = 10
)
```



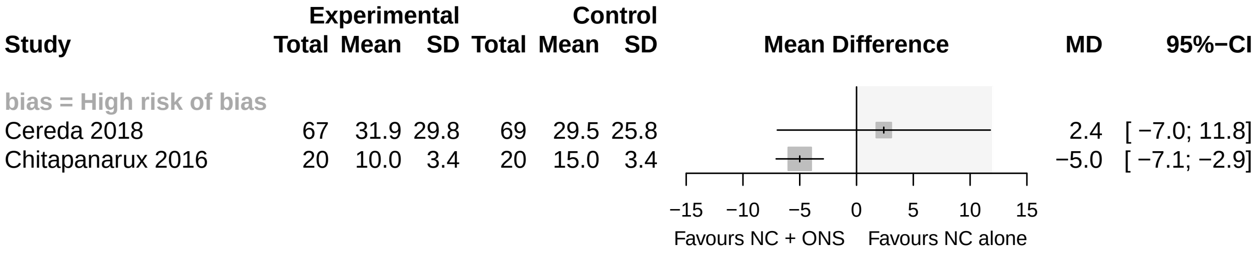
| Study | Experimental Total | Mean | SD | Control Total | Mean | SD | SMD | 95%−CI | Weight |
|---|---|---|---|---|---|---|---|---|---|
| bias = High risk of bias | | | | | | | | | |
| Cereda 2018 | 67 | 72.0 | 23.0 | 69 | 75.3 | 28.2 | −0.1 | [−0.5; 0.2] | 77.3% |
| Chitapanarux 2016 | 20 | 91.0 | 4.6 | 20 | 90.0 | 4.6 | 0.2 | [−0.4; 0.8] | 22.7% |
| **Random effects model** | **87** | | | **89** | | | **−0.1** | **[−1.9; 1.8]** | **100.0%** |

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.35$

### 4.3.3.7 Fatigue

```
QoL_Fatigue <- metacont(
  HNC$n.e,

  HNC$mean.e,

  HNC$sd.e,

  HNC$n.c,

  HNC$mean.c,

  HNC$sd.c,
```

```
  HNC$studlab,

  data = HNC,

  subset = HNC$outclab == "QoL_Fatigue" & HNC$C == 1,

  byvar = HNC$bias
)

forest(QoL_Fatigue,
       xlab="QoL_Fatigue",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 1,
       digits.se = 1,
       comb.fixed = FALSE,
       #plotwidth = "2cm"
       xlim = c(-15, 15),
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = FALSE,
       #pooled.events = TRUE,
       #resid.hetstat = FALSE,
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = C1,
       label.left = I1,
       fs.axis = 10,
       fs.lr = 10,
       lower.equi = 0, # Equivalence limits
       upper.equi = 12,
       lty.equi = 1,
       fill.equi = "#f5f5f5",
       col.equi = "white",
       overall = FALSE
)
```

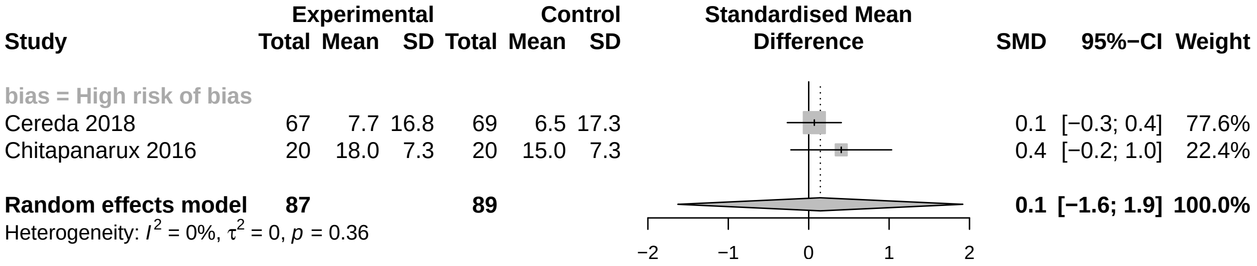


MID: 12.0 (deteriorate)

Musoro J, Coens C, Fiteni F, et al. Minimally important differences for interpreting EORTC QLQ-C30 scores in melanoma, breast cancer and head and neck cancer patients on behalf of the EORTC breast, Head and Neck, Melanoma and Quality of life groups. ISPOR Europe 2018 Barcelona, November, 2018.

#### 4.3.3.8 Financial

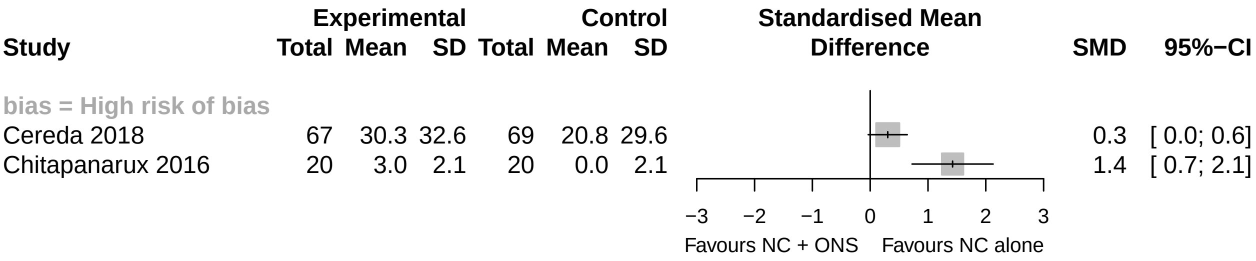
```
QoL_Financial <- metacont(
  HNC$n.e,

  HNC$mean.e,

  HNC$sd.e,

  HNC$n.c,

  HNC$mean.c,

  HNC$sd.c,

  HNC$studlab,

  data = HNC,

  subset = HNC$outclab == "QoL_Financial" & HNC$C == 1,

  byvar = HNC$bias,
  sm = "SMD",
)

forest(QoL_Financial,
       xlab="QoL_Financial",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 1,
       digits.se = 1,
       comb.fixed = FALSE,
       #plotwidth = "2cm"
       xlim = c(-2, 2),
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = TRUE,
       #pooled.events = TRUE,
       #resid.hetstat = FALSE,
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = C1,
       label.left = I1,
       fs.axis = 10,
       fs.lr = 10
)
```



#### 4.3.3.9 Insomnia

```
QoL_Insomnia <- metacont(
  HNC$n.e,

  HNC$mean.e,

  HNC$sd.e,

  HNC$n.c,

  HNC$mean.c,

  HNC$sd.c,

  HNC$studlab,

  data = HNC,

  subset = HNC$outclab == "QoL_Insomnia" & HNC$C == 1,

  byvar = HNC$bias,
  sm = "SMD",
)

forest(QoL_Insomnia,
       xlab="QoL_Insomnia",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 1,
       digits.se = 1,
       comb.fixed = FALSE,
       #plotwidth = "2cm"
       xlim = c(-3, 3),
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = FALSE,
       #pooled.events = TRUE,
       #resid.hetstat = FALSE,
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = C1,
       label.left = I1,
       fs.axis = 10,
```

```
       fs.lr = 10,
       overall = FALSE
)
```

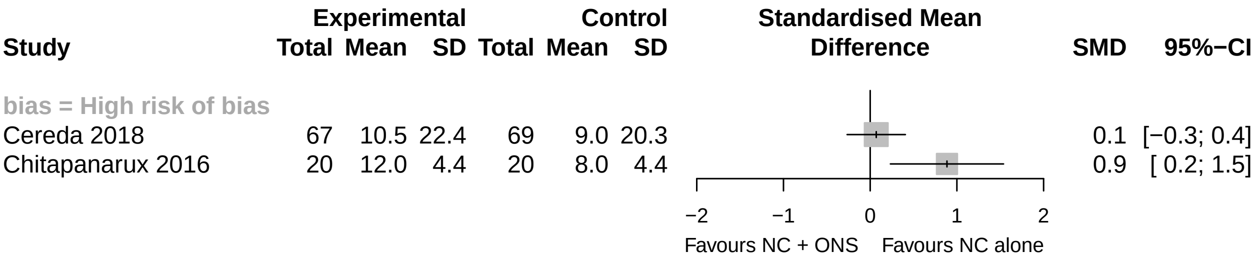


| Study | Experimental Total | Mean | SD | Control Total | Mean | SD | SMD | 95%−CI |
|---|---|---|---|---|---|---|---|---|
| bias = High risk of bias | | | | | | | | |
| Cereda 2018 | 67 | 30.3 | 32.6 | 69 | 20.8 | 29.6 | 0.3 | [ 0.0; 0.6] |
| Chitapanarux 2016 | 20 | 3.0 | 2.1 | 20 | 0.0 | 2.1 | 1.4 | [ 0.7; 2.1] |

### 4.3.3.10 Nausea

```
QoL_Nausea <- metacont(
  HNC$n.e,

  HNC$mean.e,

  HNC$sd.e,

  HNC$n.c,

  HNC$mean.c,

  HNC$sd.c,

  HNC$studlab,

  data = HNC,

  subset = HNC$outclab == "QoL_Nausea" & HNC$C == 1,

  byvar = HNC$bias,
  sm = "SMD",
)

forest(QoL_Nausea,
       xlab="QoL_Nausea",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 1,
       digits.se = 1,
       comb.fixed = FALSE,
       #plotwidth = "2cm"
       xlim = c(-2, 2),
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = FALSE,
       #pooled.events = TRUE,
       #resid.hetstat = FALSE,
```

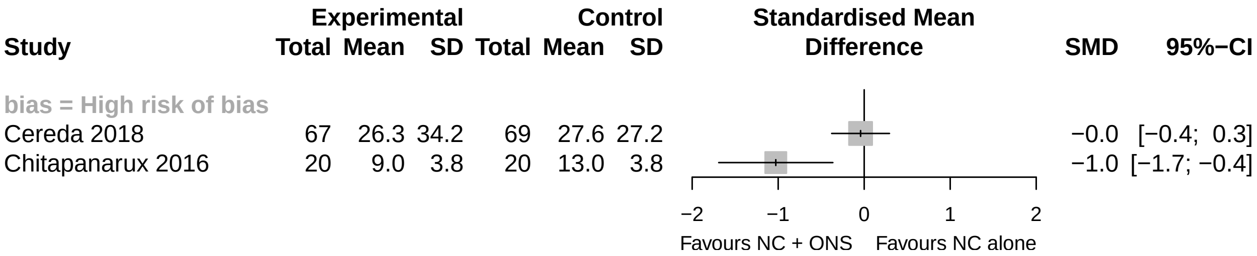
```
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = C1,
       label.left = I1,
       fs.axis = 10,
       fs.lr = 10,
       overall = FALSE
)
```



#### 4.3.3.11 Pain

```
QoL_Pain <- metacont(
  HNC$n.e,

  HNC$mean.e,

  HNC$sd.e,

  HNC$n.c,

  HNC$mean.c,

  HNC$sd.c,

  HNC$studlab,

  data = HNC,

  subset = HNC$outclab == "QoL_Pain" & HNC$C == 1,

  byvar = HNC$bias,
  sm = "SMD",
)

forest(QoL_Pain,
       xlab="QoL_Pain",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 1,
       digits.se = 1,
       comb.fixed = FALSE,
       #plotwidth = "2cm"
       xlim = c(-2, 2),
```

```
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = FALSE,
       #pooled.events = TRUE,
       #resid.hetstat = FALSE,
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = C1,
       label.left = I1,
       fs.axis = 10,
       fs.lr = 10,
       overall = FALSE
)
```

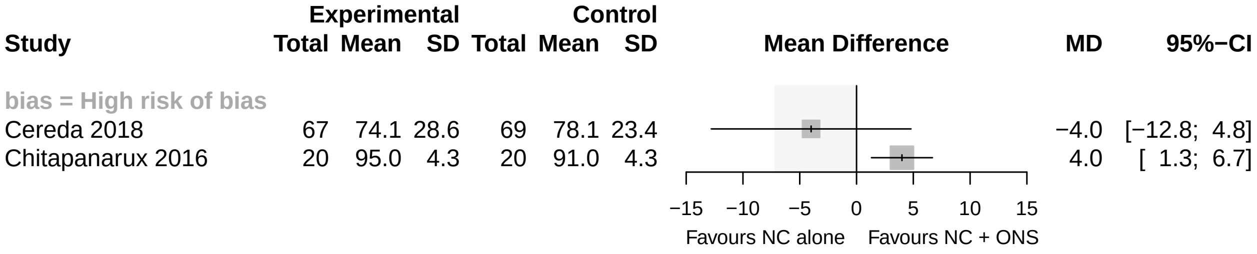


| Study | Experimental Total | Experimental Mean | Experimental SD | Control Total | Control Mean | Control SD | SMD | 95%−CI |
|---|---|---|---|---|---|---|---|---|
| bias = High risk of bias | | | | | | | | |
| Cereda 2018 | 67 | 26.3 | 34.2 | 69 | 27.6 | 27.2 | −0.0 | [−0.4; 0.3] |
| Chitapanarux 2016 | 20 | 9.0 | 3.8 | 20 | 13.0 | 3.8 | −1.0 | [−1.7; −0.4] |

#### 4.3.3.12 Physical

```
QoL_Physical <- metacont(
  HNC$n.e,

  HNC$mean.e,

  HNC$sd.e,

  HNC$n.c,

  HNC$mean.c,

  HNC$sd.c,

  HNC$studlab,

  data = HNC,

  subset = HNC$outclab == "QoL_Physical" & HNC$C == 1,

  byvar = HNC$bias,
)

forest(QoL_Physical,
       xlab="QoL_Physical",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 1,
```

```
       digits.se = 1,
       comb.fixed = FALSE,
       #plotwidth = "2cm"
       xlim = c(-15, 15),
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = FALSE,
       #pooled.events = TRUE,
       #resid.hetstat = FALSE,
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = I1,
       label.left = C1,
       fs.axis = 10,
       fs.lr = 10,
       lower.equi = -7.3, # Equivalence limits
       upper.equi = 0,
       lty.equi = 1,
       fill.equi = "#f5f5f5",
       col.equi = "white",
       overall = FALSE
)
```



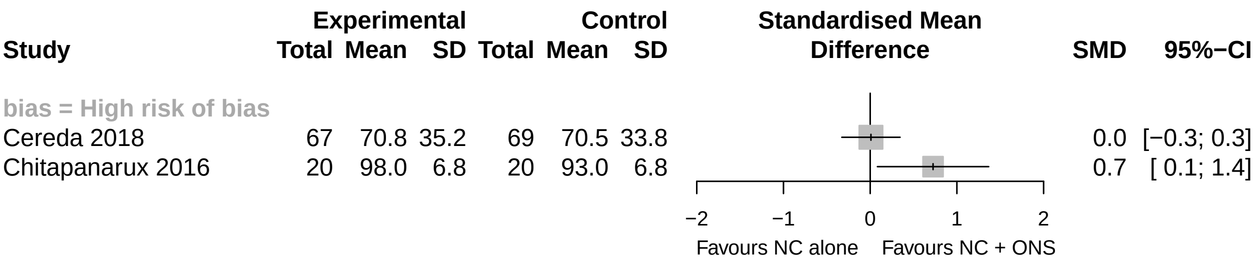
|  | Experimental |  |  | Control |  |  |  |  |
|---|---|---|---|---|---|---|---|---|
| Study | Total | Mean | SD | Total | Mean | SD | MD | 95%−CI |
| bias = High risk of bias |  |  |  |  |  |  |  |  |
| Cereda 2018 | 67 | 74.1 | 28.6 | 69 | 78.1 | 23.4 | −4.0 | [−12.8; 4.8] |
| Chitapanarux 2016 | 20 | 95.0 | 4.3 | 20 | 91.0 | 4.3 | 4.0 | [ 1.3; 6.7] |

MID: -7.3 (deteriorate)

#### 4.3.3.13 Role

```
QoL_Role <- metacont(
  HNC$n.e,

  HNC$mean.e,

  HNC$sd.e,

  HNC$n.c,

  HNC$mean.c,

  HNC$sd.c,

  HNC$studlab,

  data = HNC,

  subset = HNC$outclab == "QoL_Role" & HNC$C == 1,
```

```
  byvar = HNC$bias,
  sm = "SMD",
)

forest(QoL_Role,
       xlab="QoL_Role",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 1,
       digits.se = 1,
       comb.fixed = FALSE,
       #plotwidth = "2cm"
       xlim = c(-2, 2),
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = FALSE,
       #pooled.events = TRUE,
       #resid.hetstat = FALSE,
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = I1,
       label.left = C1,
       fs.axis = 10,
       fs.lr = 10,
       overall = FALSE
)
```

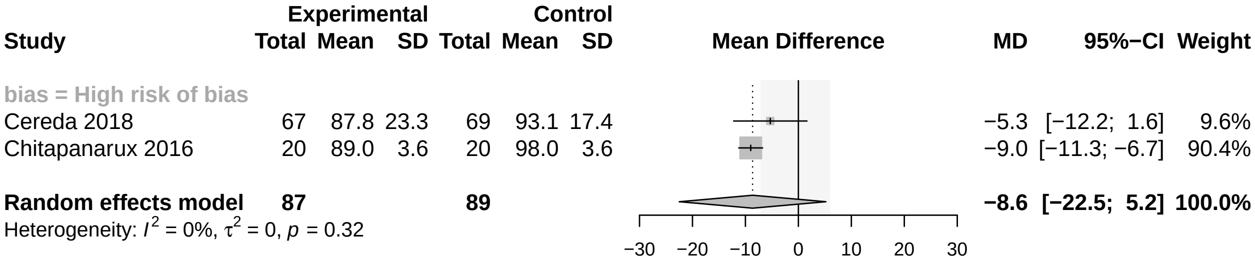


| Study | Experimental Total | Experimental Mean | Experimental SD | Control Total | Control Mean | Control SD | SMD | 95%−CI |
|---|---|---|---|---|---|---|---|---|
| bias = High risk of bias | | | | | | | | |
| Cereda 2018 | 67 | 70.8 | 35.2 | 69 | 70.5 | 33.8 | 0.0 | [−0.3; 0.3] |
| Chitapanarux 2016 | 20 | 98.0 | 6.8 | 20 | 93.0 | 6.8 | 0.7 | [ 0.1; 1.4] |

#### 4.3.3.14 Social

```
QoL_Social <- metacont(
  HNC$n.e,

  HNC$mean.e,

  HNC$sd.e,

  HNC$n.c,

  HNC$mean.c,

  HNC$sd.c,

  HNC$studlab,
```

```
  data = HNC,

  subset = HNC$outclab == "QoL_Social" & HNC$C == 1,

  byvar = HNC$bias
)

forest(QoL_Social,
       xlab="QoL_Social",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 1,
       digits.se = 1,
       comb.fixed = FALSE,
       #plotwidth = "2cm"
       xlim = c(-30, 30),
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = TRUE,
       #pooled.events = TRUE,
       #resid.hetstat = FALSE,
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = I1,
       label.left = C1,
       fs.axis = 10,
       fs.lr = 10,
       lower.equi = -7.3, # Equivalence limits
       upper.equi = 6.1,
       lty.equi = 1,
       fill.equi = "#f5f5f5",
       col.equi = "white",
)
```



| Study | Experimental Total | Experimental Mean | Experimental SD | Control Total | Control Mean | Control SD | MD | 95%−CI | Weight |
|---|---|---|---|---|---|---|---|---|---|
| bias = High risk of bias | | | | | | | | | |
| Cereda 2018 | 67 | 87.8 | 23.3 | 69 | 93.1 | 17.4 | −5.3 | [−12.2; 1.6] | 9.6% |
| Chitapanarux 2016 | 20 | 89.0 | 3.6 | 20 | 98.0 | 3.6 | −9.0 | [−11.3; −6.7] | 90.4% |
| **Random effects model** | **87** | | | **89** | | | **−8.6** | **[−22.5; 5.2]** | **100.0%** |

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.32$

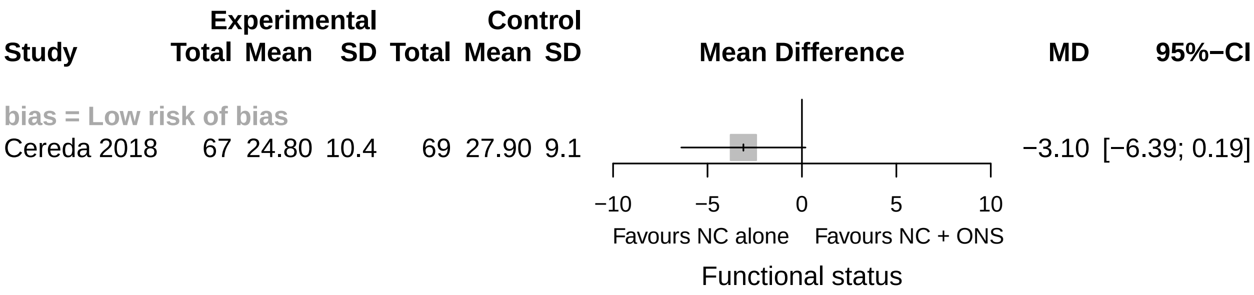
MIDs for the social functioning (SF) scale for improvement (deterioration) were SF: 6.1 (- 7.3) in HNC

Musoro J, Coens C, Fiteni F, et al. Evidence-based approach to determine meaningful change in scores of the EORTC QLQ-C30 in breast and head and neck cancer: on behalf of the EORTC Breast, Head and Neck and Quality of Life Groups. 25th annual conference of the international society for quality of life research, Dublin, Ireland. Qual Life Res 2018;27 (Suppl 1): ab101.4, 18. https://doi.org/10.1007/s11136-018-1946-9

## 4.4 Functional status (end of treatment)

### 4.4.1 Forest plot

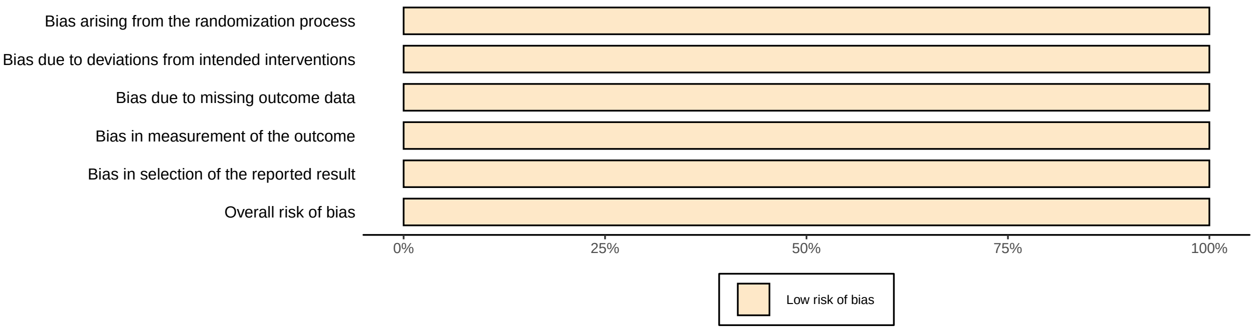
```
functional <- metacont(
  HNC$n.e,

  HNC$mean.e,

  HNC$sd.e,

  HNC$n.c,

  HNC$mean.c,

  HNC$sd.c,

  HNC$studlab,

  data = HNC,

  subset = HNC$outclab == "Functional status" & HNC$C == 1,

  byvar = HNC$bias
)

functional_d <- data.frame(functional)
rob_functional_1_1 <- merge(rob_functional_1_1, functional_d[,c("w.random", "studlab")], by = "studlab"

forest(functional,
       xlab="Functional status",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 2,
       digits.se = 1,
       comb.fixed = FALSE,
       xlim = c(-10,10),
       #plotwidth = "2cm",
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = TRUE,
       #pooled.events = TRUE,
       #resid.hetstat = FALSE,
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = I1,
       label.left = C1,
       fs.axis = 10,
       fs.lr = 10
)
```



### 4.4.2 Proportion of information at each level of risk of bias

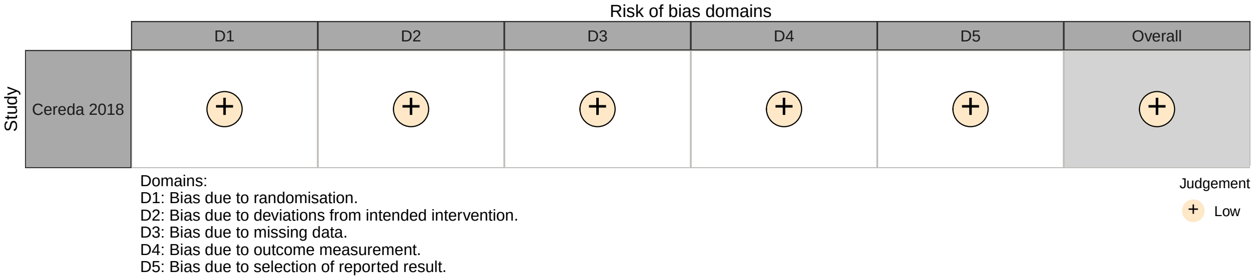
Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)

```r
rob_summary(rob_functional_1_1, tool = "ROB2", weighted = TRUE, overall = TRUE, colour = "colourblind")
```



### 4.4.3 Risk of bias assessments by study

```r
rob_traffic_light(rob_functional_1_1, tool = "ROB2", colour = "colourblind", psize = 10)
```



Domains:
D1: Bias due to randomisation.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing data.
D4: Bias due to outcome measurement.
D5: Bias due to selection of reported result.

## 4.5 Body weight (end of treatment)

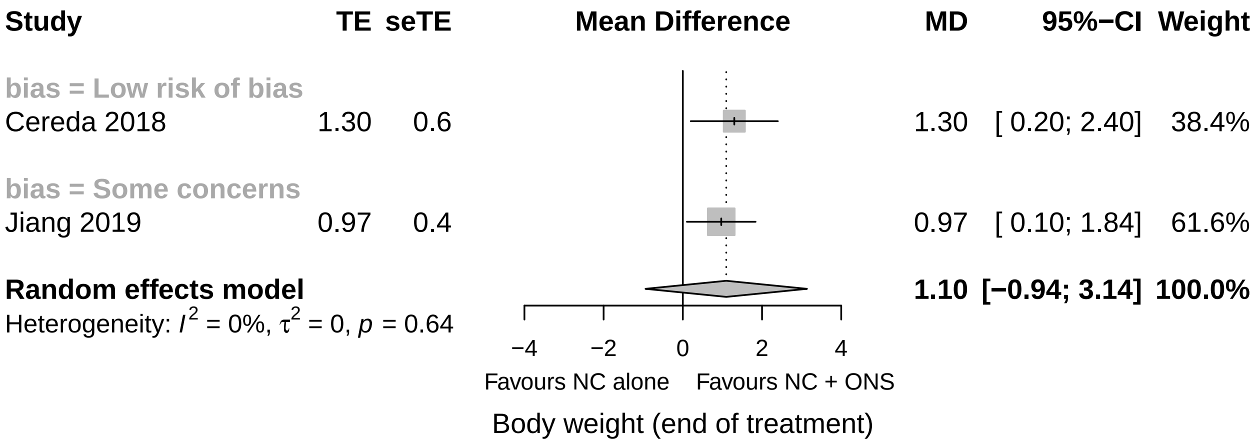
### 4.5.1 Main analysis

Including only results at most at some concerns of bias.

#### 4.5.1.1 Forest plot

```r
bw_1_1 <- metagen(
  HNC$TE,
```

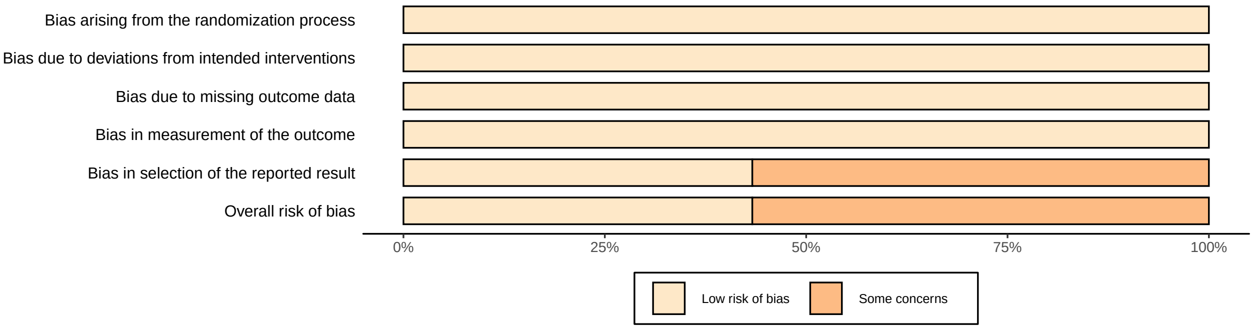
```r
  HNC$seTE,
  sm = "MD",
  HNC$studlab,
  data = HNC,
  subset = HNC$outclab == "Body weight" & HNC$C == 1,
  byvar = HNC$bias,
)

bw_1_1_d <- data.frame(bw_1_1)
rob_bw_1_1 <- merge(rob_bw_1_1, bw_1_1_d[,c("w.random", "studlab")], by = "studlab", all = TRUE)
rob_bw_1_1_S <- subset(rob_bw_1_1, Overall != "High")
rob_bw_1_1_S_2 <- subset(rob_bw_1_1,studlab != "Chitapanarux 2016")

bw_1_1_LB <- update.meta(bw_1_1, subset = HNC$outclab == "Body weight" & HNC$C == 1 & HNC$bias != "High

forest(bw_1_1_LB,
       xlab="Body weight (end of treatment)",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 2,
       digits.se = 1,
       comb.fixed = FALSE,
       xlim = c(-5, 5),
       #leftcols = c("studlab", "n.e", "n.c", "TE", "seTE", "random.w"),
       #xlim    = "s",
       #plotwidth = "2cm",
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = TRUE,
       #pooled.events = TRUE,
       #resid.hetstat = FALSE,
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = I1,
       label.left = C1,
       fs.axis = 10,
       fs.lr = 10
)
```



#### 4.5.1.2 Proportion of information at each level of risk of bias

Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)

```
rob_summary(rob_bw_1_1_S, tool = "ROB2", weighted = TRUE, overall = TRUE, colour = "colourblind")
```



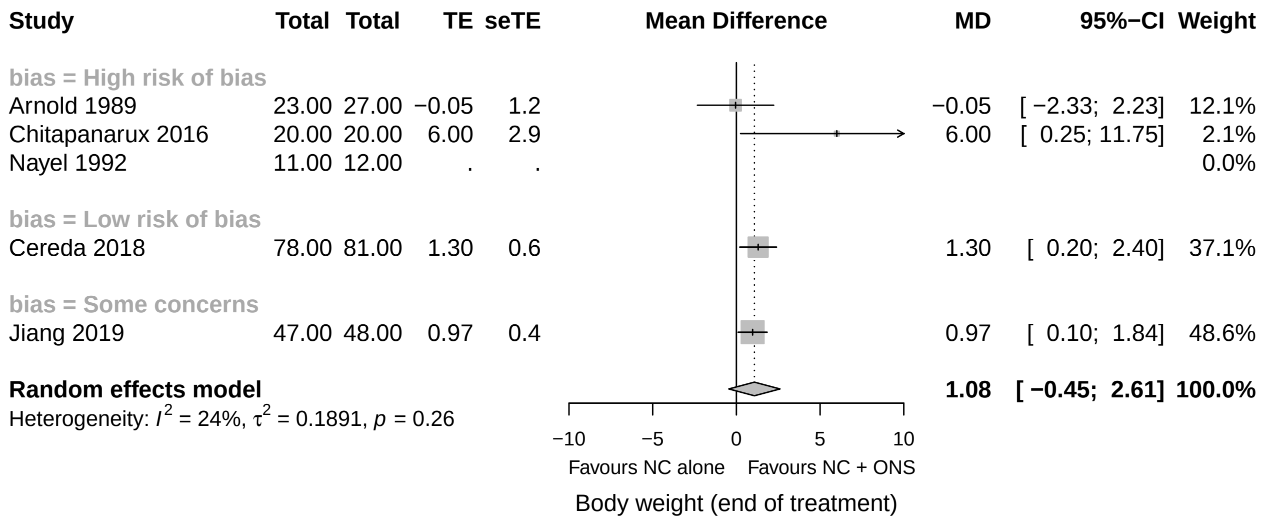
### 4.5.2 Sensitivity analysis 1

Including all available results.

#### 4.5.2.1 Forest plot

```
forest(bw_1_1,
       xlab="Body weight (end of treatment)",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 2,
       digits.se = 1,
       comb.fixed = FALSE,
       xlim = c(-10, 10),
       leftcols = c("studlab", "n.e", "n.c", "TE", "seTE"),
       #xlim    = "s",
       #plotwidth = "2cm",
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = TRUE,
       #pooled.events = TRUE,
```

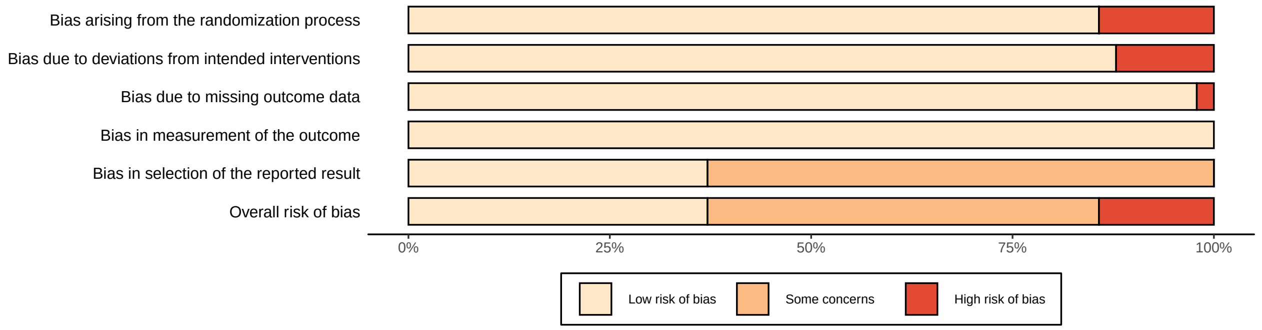
```
        #resid.hetstat = FALSE,
        colgap.forest = "0.5 cm",
        just = "right",
        label.right = I1,
        label.left = C1,
        fs.axis = 10,
        fs.lr = 10
)
```



### 4.5.2.2 Proportion of information at each level of risk of bias

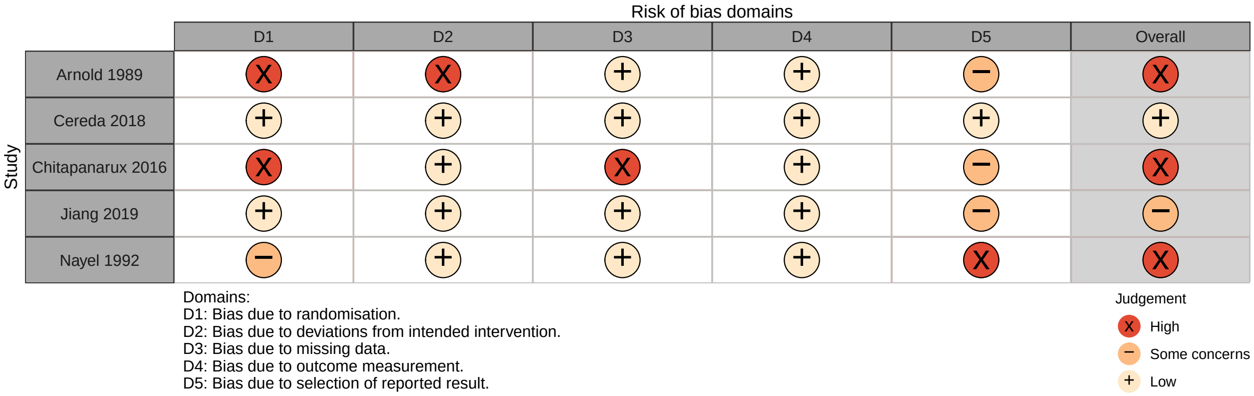
Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)

```
rob_summary(rob_bw_1_1, tool = "ROB2", weighted = TRUE, overall = TRUE, colour = "colourblind")
```



### 4.5.2.3 Risk of bias assessments by study

```
rob_traffic_light(rob_bw_1_1, tool = "ROB2", colour = "colourblind", psize = 10)
```



Risk of bias domains

| Study | D1 | D2 | D3 | D4 | D5 | Overall |
|---|---|---|---|---|---|---|
| Arnold 1989 | X | X | + | + | − | X |
| Cereda 2018 | + | + | + | + | + | + |
| Chitapanarux 2016 | X | + | X | + | − | X |
| Jiang 2019 | + | + | + | + | − | − |
| Nayel 1992 | − | + | + | + | X | X |

Domains:
D1: Bias due to randomisation.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing data.
D4: Bias due to outcome measurement.
D5: Bias due to selection of reported result.

Judgement
X High
− Some concerns
\+ Low

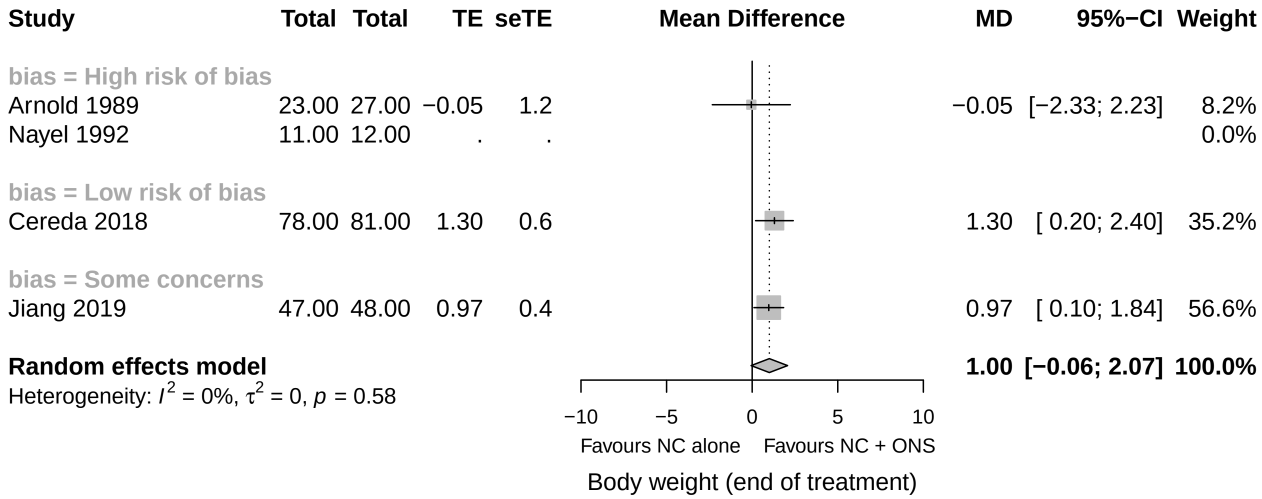
```
#forest(metainf(bw_1_1,
#                pooled = "random"))
```

### 4.5.3 Sensitivity analysis 2

Excluding Chitapanarux 2016, because mean and standard deviation for this study were inputted (as described in the methods section of the primary report).

#### 4.5.3.1 Forest plot

```
bw_1_1_S_2 <- update.meta(bw_1_1, subset = HNC$outclab == "Body weight" & HNC$C == 1 & HNC$studlab != "

forest(bw_1_1_S_2,
       xlab="Body weight (end of treatment)",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 2,
       digits.se = 1,
       comb.fixed = FALSE,
       xlim = c(-10, 10),
       leftcols = c("studlab", "n.e", "n.c", "TE", "seTE"),
       #xlim    = "s",
       #plotwidth = "2cm",
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = TRUE,
       #pooled.events = TRUE,
       #resid.hetstat = FALSE,
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = I1,
       label.left = C1,
       fs.axis = 10,
       fs.lr = 10
)
```



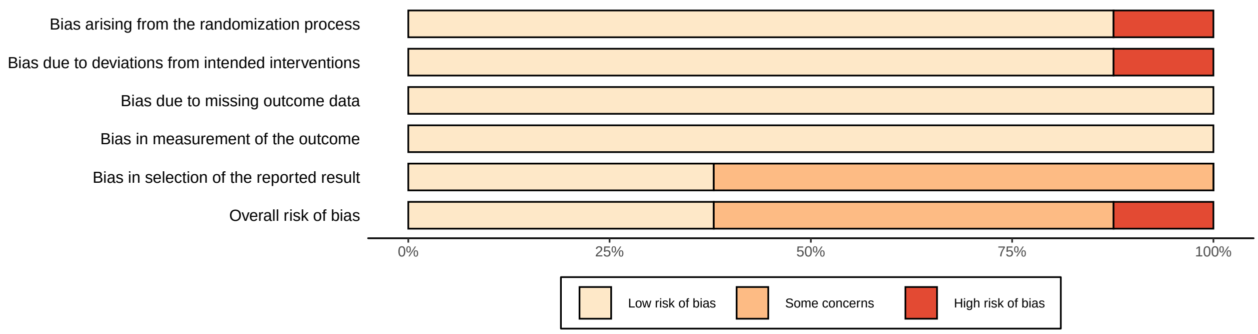
| Study | Total | Total | TE | seTE | MD | 95%−CI | Weight |
|---|---|---|---|---|---|---|---|
| bias = High risk of bias | | | | | | | |
| Arnold 1989 | 23.00 | 27.00 | −0.05 | 1.2 | −0.05 | [−2.33; 2.23] | 8.2% |
| Nayel 1992 | 11.00 | 12.00 | . | . | | | 0.0% |
| bias = Low risk of bias | | | | | | | |
| Cereda 2018 | 78.00 | 81.00 | 1.30 | 0.6 | 1.30 | [ 0.20; 2.40] | 35.2% |
| bias = Some concerns | | | | | | | |
| Jiang 2019 | 47.00 | 48.00 | 0.97 | 0.4 | 0.97 | [ 0.10; 1.84] | 56.6% |
| **Random effects model** | | | | | **1.00** | **[−0.06; 2.07]** | **100.0%** |

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.58$

### 4.5.3.2 Proportion of information at each level of risk of bias

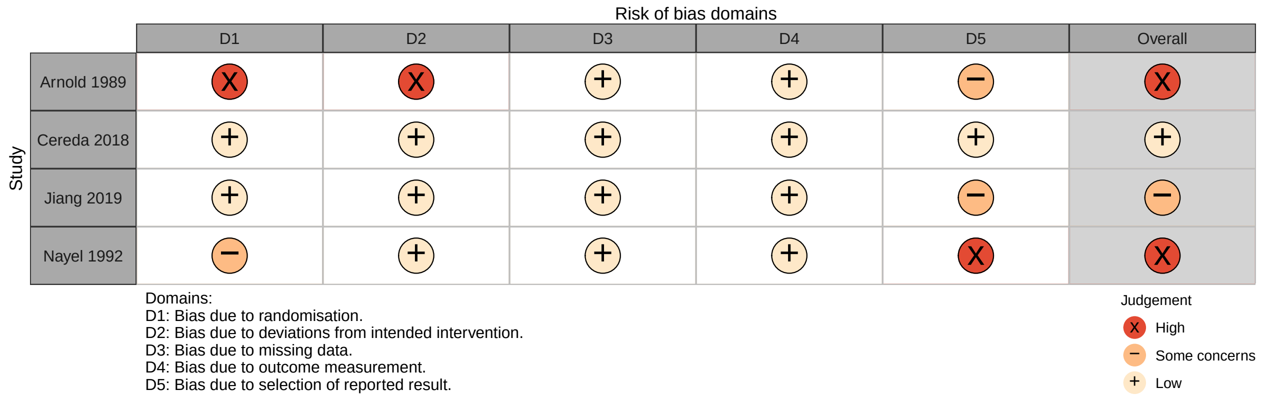
Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)

```
rob_summary(rob_bw_1_1_S_2, tool = "ROB2", weighted = TRUE, overall = TRUE, colour = "colourblind")
```



### 4.5.3.3 Risk of bias assessments by study

```
rob_traffic_light(rob_bw_1_1_S_2, tool = "ROB2", colour = "colourblind", psize = 10)
```



| | D1 | D2 | D3 | D4 | D5 | Overall |
|---|---|---|---|---|---|---|
| Arnold 1989 | X | X | + | + | − | X |
| Cereda 2018 | + | + | + | + | + | + |
| Jiang 2019 | + | + | + | + | − | − |
| Nayel 1992 | − | + | + | + | X | X |

Domains:
D1: Bias due to randomisation.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing data.
D4: Bias due to outcome measurement.
D5: Bias due to selection of reported result.

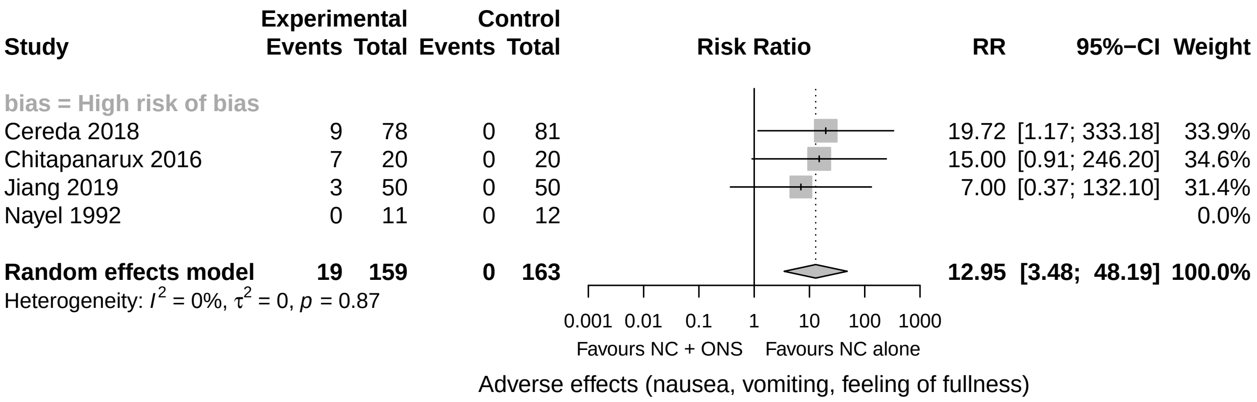
Judgement
X High
− Some concerns
+ Low

```
#forest(metainf(bw_1_1,
#                pooled = "random"))
```

## 4.6 Adverse effects

### 4.6.1 Forest plot

```
ae <- metabin(
  HNC$event.e,
  HNC$n.e,
  HNC$event.c,
  HNC$n.c,
  sm = "RR",
  method = "MH",
  RR.cochrane = TRUE,
  MH.exact = FALSE,
  allstudies = FALSE,
  HNC$studlab,
  subset = HNC$outclab == "Adverse events" & HNC$C == 1,
  byvar = HNC$bias,
)

ae_d <- data.frame(ae)
rob_ae_1 <- merge(rob_ae_1, ae_d[,c("w.random", "studlab")], by = "studlab", all = TRUE)

forest(ae,
       xlab="Adverse effects (nausea, vomiting, feeling of fullness)",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 2,
       digits.se = 1,
       comb.fixed = FALSE,
       xlim = c(0.001, 1000),
       #xlim    = "s",
       #plotwidth = "2cm",
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = TRUE,
       pooled.events = TRUE,
       #resid.hetstat = FALSE,
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = C1,
       label.left = I1,
       fs.axis = 10,
       fs.lr = 10
)
```



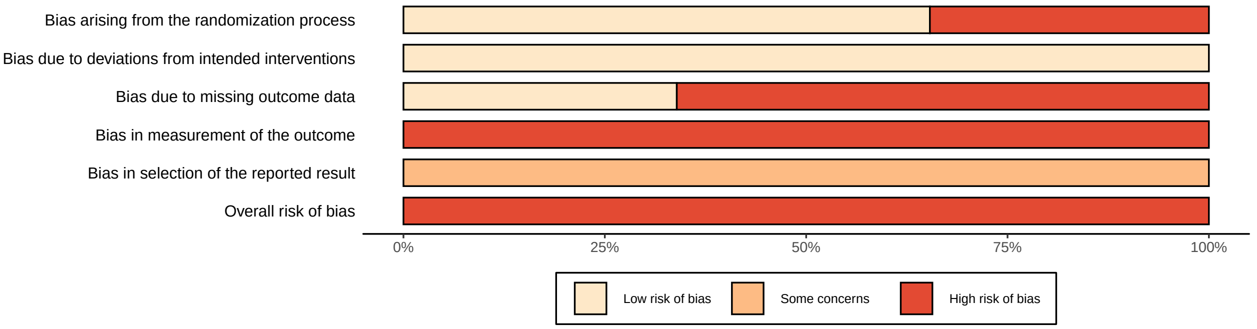
| Study | Experimental Events | Experimental Total | Control Events | Control Total | RR | 95%−CI | Weight |
|---|---|---|---|---|---|---|---|
| bias = High risk of bias | | | | | | | |
| Cereda 2018 | 9 | 78 | 0 | 81 | 19.72 | [1.17; 333.18] | 33.9% |
| Chitapanarux 2016 | 7 | 20 | 0 | 20 | 15.00 | [0.91; 246.20] | 34.6% |
| Jiang 2019 | 3 | 50 | 0 | 50 | 7.00 | [0.37; 132.10] | 31.4% |
| Nayel 1992 | 0 | 11 | 0 | 12 | | | 0.0% |
| **Random effects model** | **19** | **159** | **0** | **163** | **12.95** | **[3.48; 48.19]** | **100.0%** |

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.87$

### 4.6.2 Proportion of information at each level of risk of bias

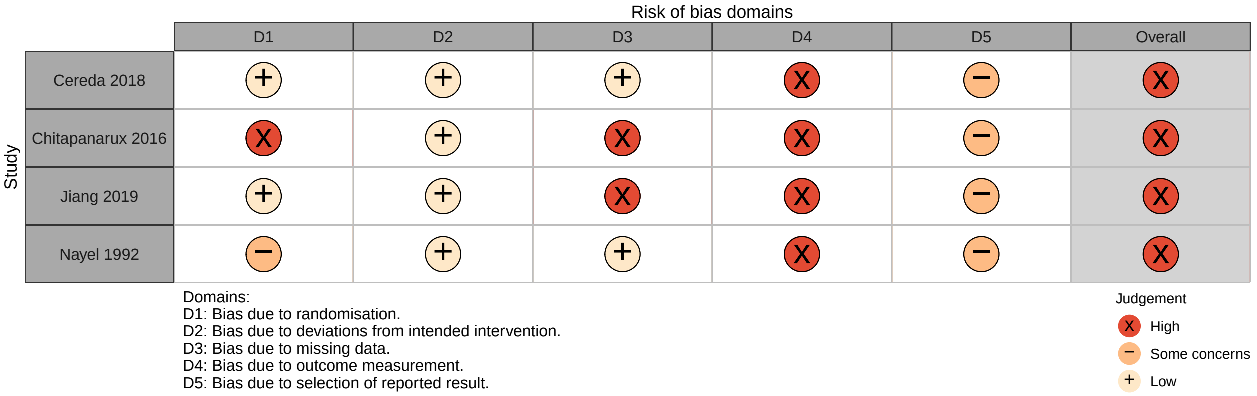
Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)

```r
rob_summary(rob_ae_1, tool = "ROB2", weighted = TRUE, overall = TRUE, colour = "colourblind")
```



### 4.6.3 Risk of bias assessments by study

```r
rob_traffic_light(rob_ae_1, tool = "ROB2", colour = "colourblind", psize = 10)
```



Risk of bias domains

| Study | D1 | D2 | D3 | D4 | D5 | Overall |
|---|---|---|---|---|---|---|
| Cereda 2018 | + | + | + | X | − | X |
| Chitapanarux 2016 | X | + | X | X | − | X |
| Jiang 2019 | + | + | X | X | − | X |
| Nayel 1992 | − | + | + | X | − | X |

Domains:
D1: Bias due to randomisation.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing data.
D4: Bias due to outcome measurement.
D5: Bias due to selection of reported result.

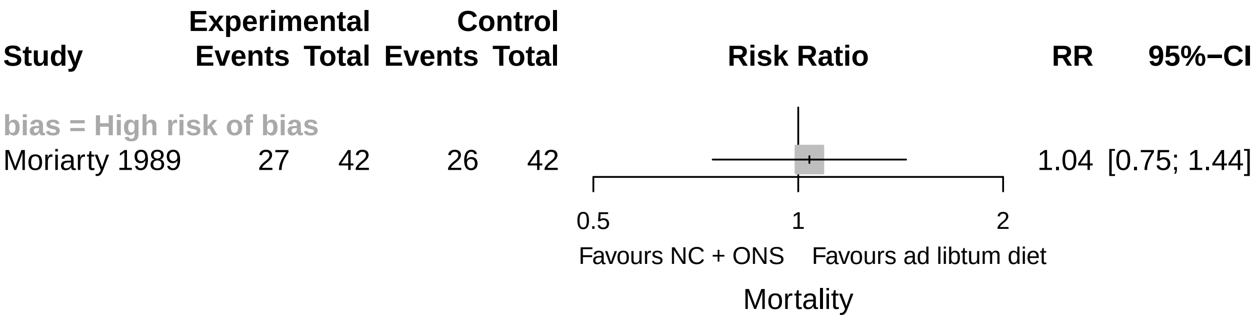
Judgement
X High
− Some concerns
\+ Low

# 5 Comparison 2

## 5.1 Mortality

### 5.1.1 Forest plot

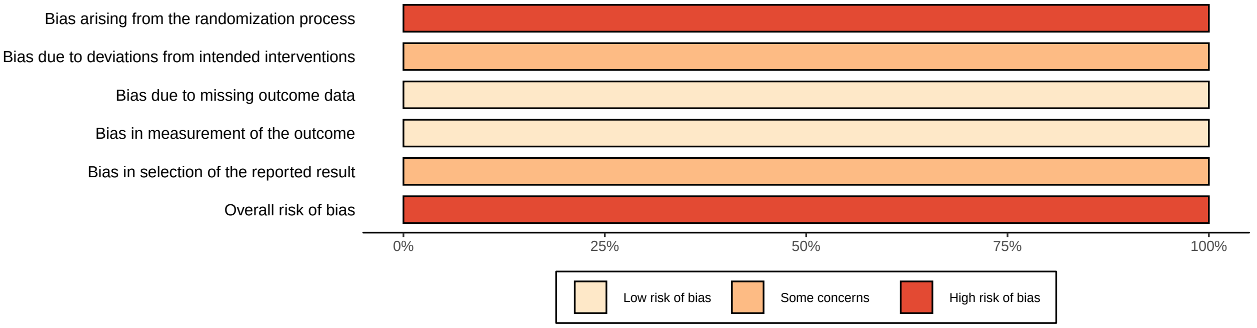
```r
mort_2 <- metabin(
  HNC$event.e,
  HNC$n.e,
  HNC$event.c,
  HNC$n.c,
  sm = "RR",
  method = "MH",
  RR.cochrane = TRUE,
  MH.exact = FALSE,
  allstudies = FALSE,
  HNC$studlab,
  subset = HNC$outclab == "Mortality" & HNC$C == 2,
  byvar = HNC$bias
)

mort_2d <- data.frame(mort_2)
rob_mort_2 <- merge(rob_mort_2, mort_2d[,c("w.random", "studlab")], by = "studlab", all = TRUE)

forest(mort_2,
       xlab="Mortality",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 2,
       digits.se = 1,
       comb.fixed = FALSE,
       xlim = c(0.5, 2),
       #xlim    = "s",
       #plotwidth = "2cm",
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = TRUE,
       #pooled.events = TRUE,
       #resid.hetstat = FALSE,
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = C1,
       label.left = I1,
       fs.axis = 10,
       fs.lr = 10
)
```



### 5.1.2 Proportion of information at each level of risk of bias

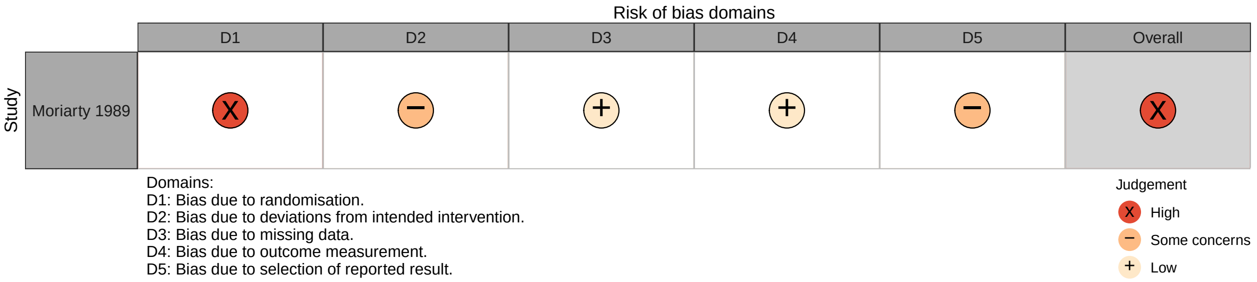
Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)

```r
rob_summary(rob_mort_2, tool = "ROB2", weighted = TRUE, overall = TRUE, colour = "colourblind")
```



### 5.1.3 Risk of bias assessments by study

```r
rob_traffic_light(rob_mort_2, tool = "ROB2", colour = "colourblind", psize = 10)
```



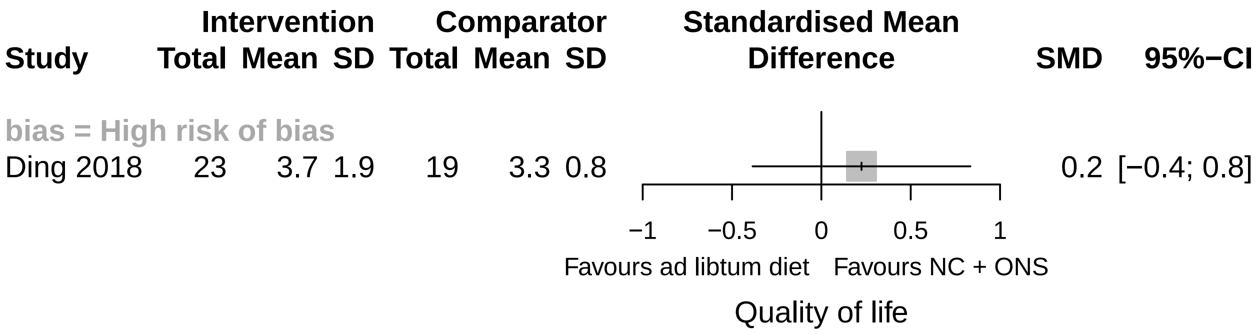
## 5.2 Quality of life (end of treatment)

### 5.2.1 Global quality of life

#### 5.2.1.1 Forest plot

```r
QoL_2 <- metacont(
  HNC$n.e,

  HNC$mean.e,
```

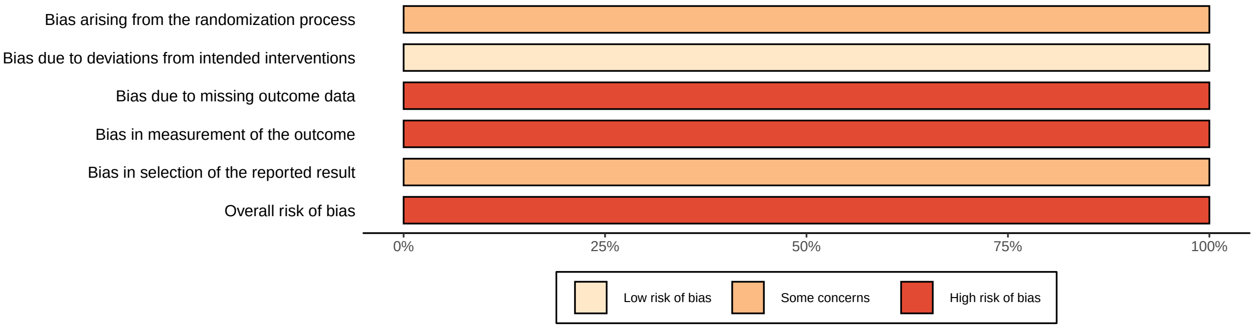
```
  HNC$sd.e,

  HNC$n.c,

  HNC$mean.c,

  HNC$sd.c,

  HNC$studlab,

  data = HNC,

  subset = HNC$outclab == "QoL" & HNC$C == 2,

  sm = "SMD",
  byvar = HNC$bias
)

QoL_2_d <- data.frame(QoL_2)
rob_QoL_2_1 <- merge(rob_QoL_2_1, QoL_2_d[,c("w.random", "studlab")], by = "studlab", all = TRUE)

forest(QoL_2,
       xlab="Quality of life",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 1,
       digits.se = 1,
       comb.fixed = FALSE,
       plotwidth = "5cm",
       xlim = c(-1, 1),
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = TRUE,
       #pooled.events = TRUE,
       #resid.hetstat = FALSE,
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = I1,
       label.left = C1,
       fs.axis = 10,
       fs.lr = 10,
       lab.e = "Intervention",
       lab.c = "Comparator",
)
```



#### 5.2.1.2 Proportion of information at each level of risk of bias

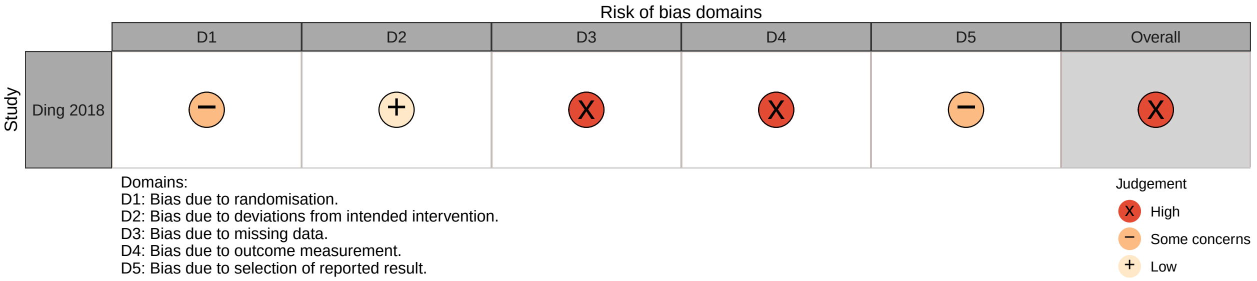
Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)

```r
rob_summary(rob_QoL_2_1, tool = "ROB2", weighted = TRUE, overall = TRUE, colour = "colourblind")
```



#### 5.2.1.3 Risk of bias assessments by study

```r
rob_traffic_light(rob_QoL_2_1, tool = "ROB2", colour = "colourblind", psize = 10)
```

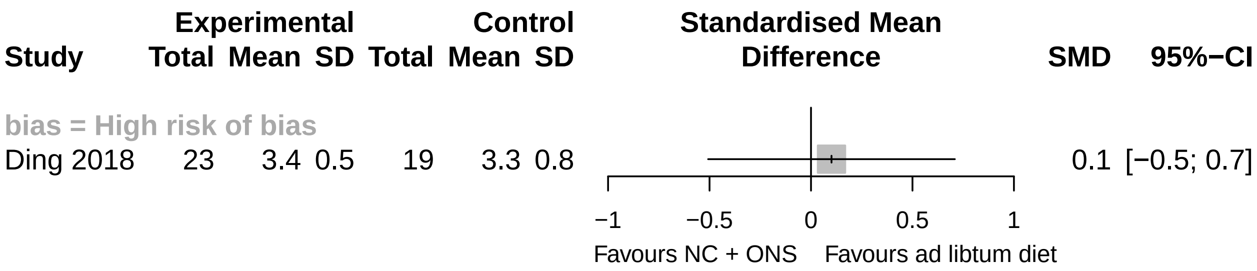


### 5.2.2 Quality of life subscales

#### 5.2.2.1 Appetite loss

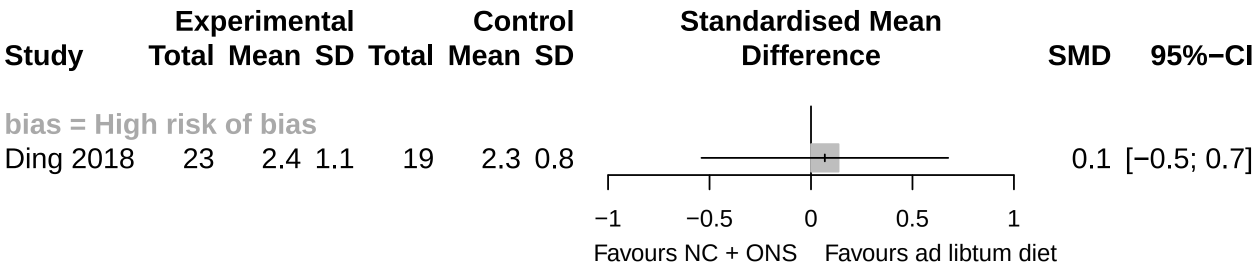
```r
QoL_Appetite_2 <- metacont(
  HNC$n.e,

  HNC$mean.e,
```

```
  HNC$sd.e,

  HNC$n.c,

  HNC$mean.c,

  HNC$sd.c,

  HNC$studlab,

  data = HNC,

  subset = HNC$outclab == "QoL_Appetite" & HNC$C == 2,

  sm = "SMD",
  byvar = HNC$bias
)

forest(QoL_Appetite_2,
       xlab="QoL_Appetite",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 1,
       digits.se = 1,
       comb.fixed = FALSE,
       xlim = c(-1,1),
       #plotwidth = "2cm",
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = TRUE,
       #pooled.events = TRUE,
       #resid.hetstat = FALSE,
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = C1,
       label.left = I1,
       fs.axis = 10,
       fs.lr = 10
)
```



#### 5.2.2.2 Constipation

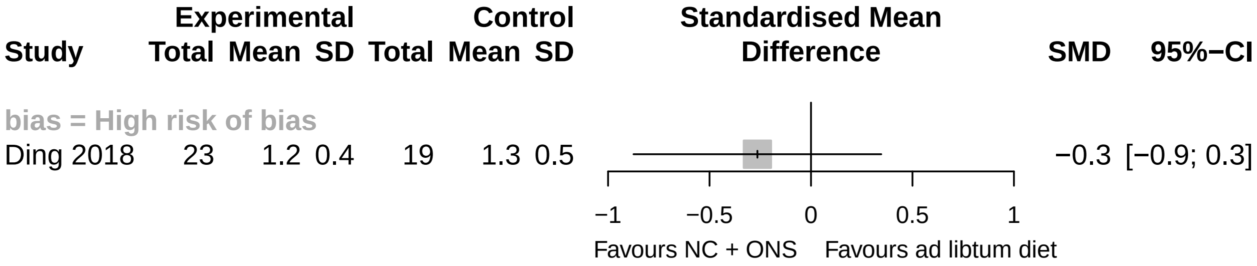
```
QoL_Constipation_2 <- metacont(
  HNC$n.e,

  HNC$mean.e,

  HNC$sd.e,

  HNC$n.c,

  HNC$mean.c,

  HNC$sd.c,

  HNC$studlab,

  data = HNC,

  subset = HNC$outclab == "QoL_Constipation" & HNC$C == 2,

  sm = "SMD",
  byvar = HNC$bias
)

forest(QoL_Constipation_2,
       xlab="QoL_Constipation",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 1,
       digits.se = 1,
       comb.fixed = FALSE,
       #plotwidth = "2cm"
       xlim = c(-1,1),
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = TRUE,
       #pooled.events = TRUE,
       #resid.hetstat = FALSE,
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = C1,
       label.left = I1,
       fs.axis = 10,
       fs.lr = 10
)
```



#### 5.2.2.3 Diarrhoea

```
QoL_Diarrhoea_2 <- metacont(
  HNC$n.e,

  HNC$mean.e,

  HNC$sd.e,

  HNC$n.c,

  HNC$mean.c,

  HNC$sd.c,

  HNC$studlab,

  data = HNC,

  subset = HNC$outclab == "QoL_Diarrhoea" & HNC$C == 2,

  sm = "SMD",
  byvar = HNC$bias
)

forest(QoL_Diarrhoea_2,
       xlab="QoL_Diarrhoea",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 1,
       digits.se = 1,
       comb.fixed = FALSE,
       #plotwidth = "2cm"
       xlim = c(-1,1),
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = TRUE,
       #pooled.events = TRUE,
       #resid.hetstat = FALSE,
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = C1,
       label.left = I1,
       fs.axis = 10,
```

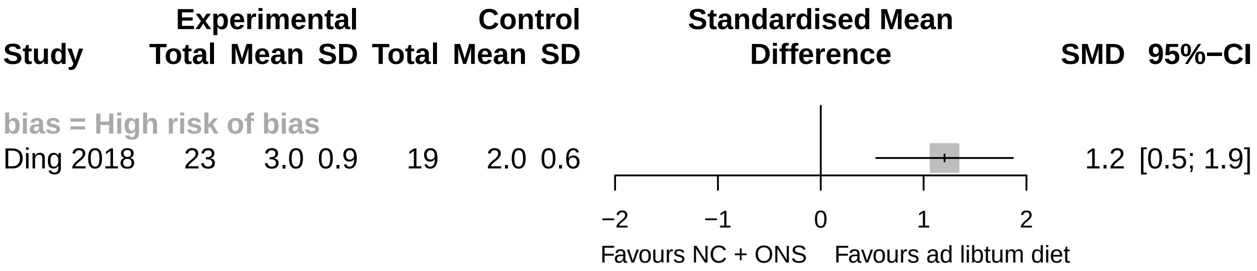
```
       fs.lr = 10
)
```



#### 5.2.2.4 Nausea

```
QoL_Nausea_2 <- metacont(
  HNC$n.e,

  HNC$mean.e,

  HNC$sd.e,

  HNC$n.c,

  HNC$mean.c,

  HNC$sd.c,

  HNC$studlab,

  data = HNC,

  subset = HNC$outclab == "QoL_Nausea" & HNC$C == 2,

  sm = "SMD",
  byvar = HNC$bias
)

forest(QoL_Nausea_2,
       xlab="QoL_Nausea",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 1,
       digits.se = 1,
       comb.fixed = FALSE,
       #plotwidth = "2cm"
       xlim = c(-2,2),
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = TRUE,
       #pooled.events = TRUE,
       #resid.hetstat = FALSE,
       colgap.forest = "0.5 cm",
```

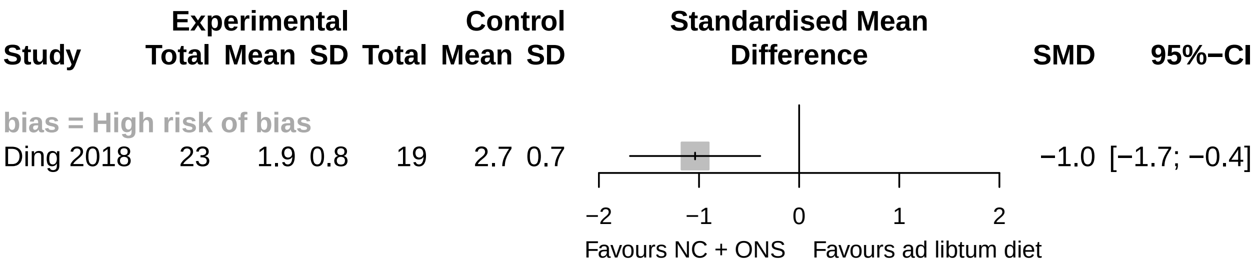
```
       just = "right",
       label.right = C1,
       label.left = I1,
       fs.axis = 10,
       fs.lr = 10
)
```



#### 5.2.2.5 Pain

```
QoL_Pain_2 <- metacont(
  HNC$n.e,

  HNC$mean.e,

  HNC$sd.e,

  HNC$n.c,

  HNC$mean.c,

  HNC$sd.c,

  HNC$studlab,

  data = HNC,

  subset = HNC$outclab == "QoL_Pain" & HNC$C == 2,

  sm = "SMD",
  byvar = HNC$bias
)

forest(QoL_Pain_2,
       xlab="QoL_Pain",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 1,
       digits.se = 1,
       comb.fixed = FALSE,
       #plotwidth = "2cm"
       xlim = c(-2,2),
       subgroup = FALSE,
       hetstat = FALSE,
```

```
       overall.hetstat = TRUE,
       #pooled.events = TRUE,
       #resid.hetstat = FALSE,
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = C1,
       label.left = I1,
       fs.axis = 10,
       fs.lr = 10
)
```

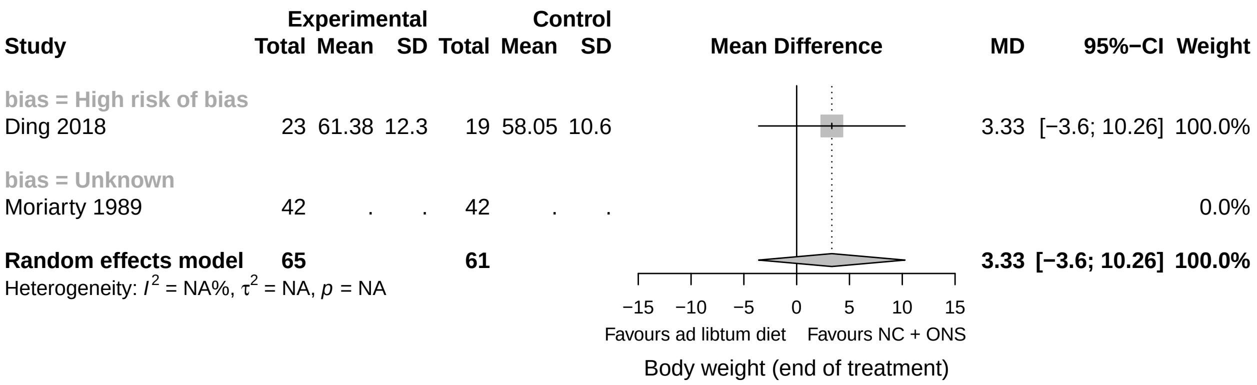


## 5.3 Body weight (end of treatment)

### 5.3.1 Forest plot

```
bw_2_1 <- metacont(
  HNC$n.e,
  HNC$mean.e,
  HNC$sd.e,
  HNC$n.c,
  HNC$mean.c,
  HNC$sd.c,
  HNC$studlab,
  data = HNC,
  subset = HNC$outclab == "Body weight" & HNC$C == 2,
  byvar = HNC$bias,
)

bw_2_1_d <- data.frame(bw_2_1)
rob_bw_2_1 <- merge(rob_bw_2_1, bw_2_1_d[,c("w.random", "studlab")], by = "studlab", all = TRUE)
rob_bw_2_1_x <- subset(rob_bw_2_1, studlab != "Moriarty 1989")

forest(bw_2_1,
       xlab="Body weight (end of treatment)",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 2,
       digits.se = 1,
       comb.fixed = FALSE,
       xlim = c(-15, 15),
       #leftcols = c("studlab", "n.e", "n.c", "TE", "seTE", "random.w"),
       #xlim    = "s",
       #plotwidth = "2cm",
```

```
        subgroup = FALSE,
        hetstat = FALSE,
        overall.hetstat = TRUE,
        #pooled.events = TRUE,
        #resid.hetstat = FALSE,
        colgap.forest = "0.5 cm",
        just = "right",
        label.right = I1,
        label.left = C1,
        fs.axis = 10,
        fs.lr = 10
)
```

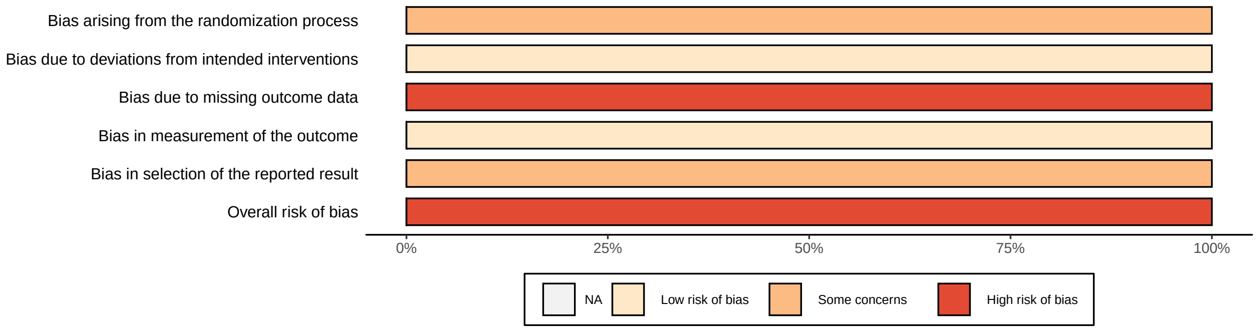


Moriarty 1981 measured body weight but only reported the result as statistically non-significant, so it could not be included in a meta-analysis.

### 5.3.2 Proportion of information at each level of risk of bias

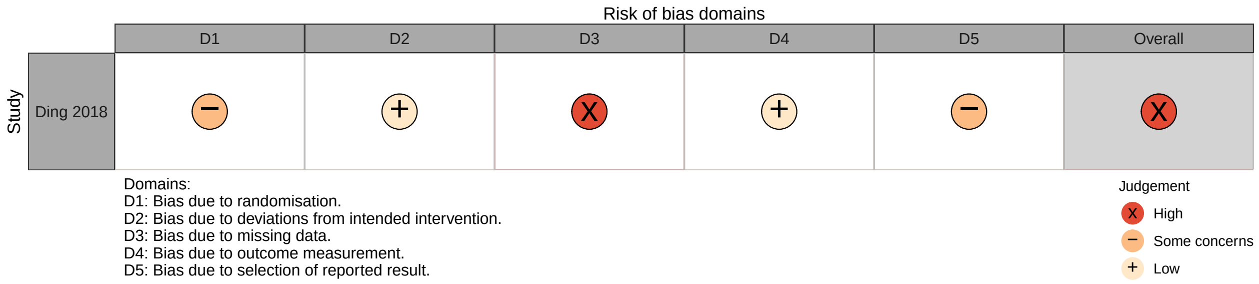
Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)

```
rob_summary(rob_bw_2_1, tool = "ROB2", weighted = TRUE, overall = TRUE, colour = "colourblind")
```



### 5.3.3 Risk of bias assessments by study

```
rob_traffic_light(rob_bw_2_1_x, tool = "ROB2", colour = "colourblind", psize = 10)
```



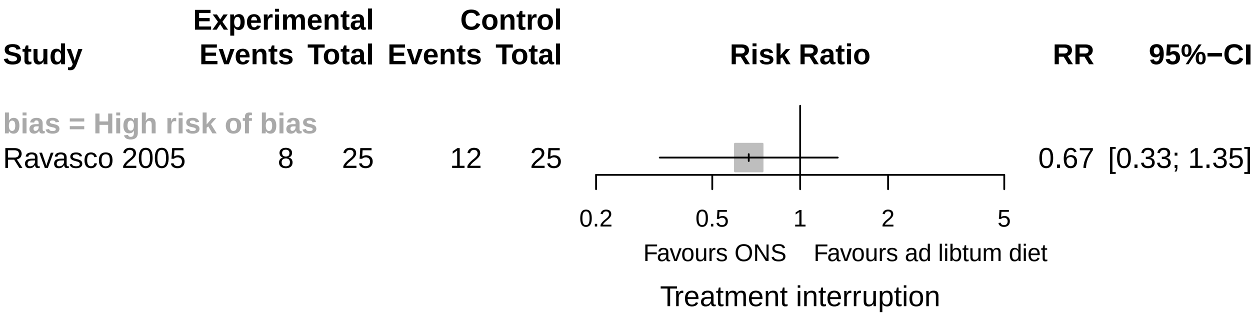
# 6 Comparison 3

## 6.1 Mortality

### 6.1.1 Forest plot

```
mort_3 <- metabin(
  HNC$event.e,
  HNC$n.e,
  HNC$event.c,
  HNC$n.c,
  sm = "RR",
  method = "MH",
  RR.cochrane = TRUE,
  MH.exact = FALSE,
  allstudies = TRUE,
  HNC$studlab,
  subset = HNC$outclab == "Mortality" & HNC$C == 3,
  byvar = HNC$bias,
  comb.fixed = FALSE,
)

mort_3_d <- data.frame(mort_3)
rob_mort_3 <- merge(rob_mort_3, mort_3_d[,c("w.random", "studlab")], by = "studlab", all = TRUE)

forest(mort_3,
       xlab="Treatment interruption",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 2,
       digits.se = 1,
       comb.fixed = FALSE,
       #overall = FALSE,
       #subgroup = FALSE,
       xlim = c(0.2, 5),
       #xlim    = "s",
       #plotwidth = "2cm",
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = TRUE,
       #pooled.events = TRUE,
```

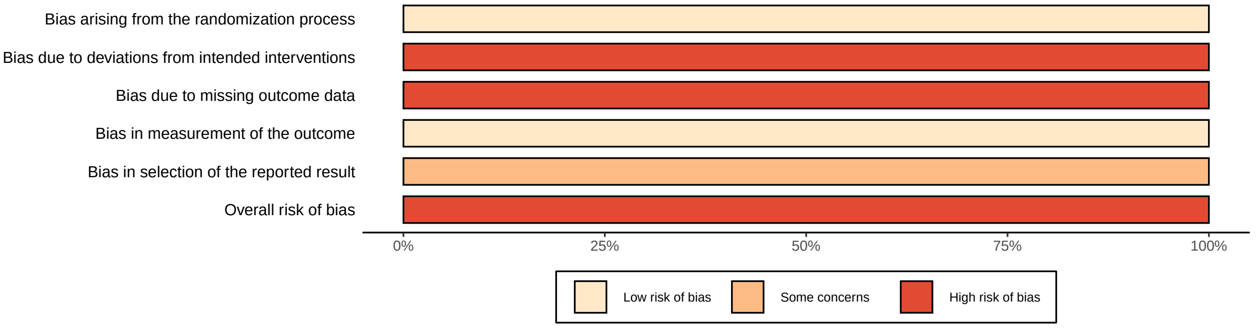
```
        #resid.hetstat = FALSE,
        colgap.forest = "0.5 cm",
        just = "right",
        label.right = C1,
        label.left = I1,
        fs.axis = 10,
        fs.lr = 10
)
```



### 6.1.2 Proportion of information at each level of risk of bias

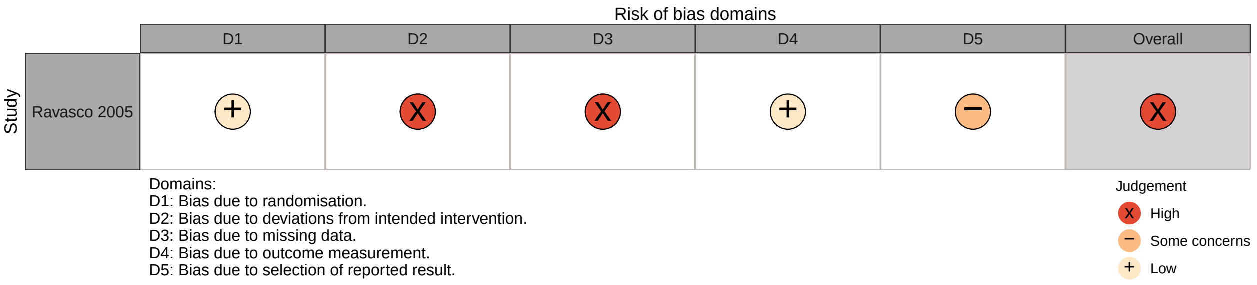
Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)

```
rob_summary(rob_mort_3, tool = "ROB2", weighted = FALSE, overall = TRUE, colour = "colourblind")
```



### 6.1.3 Risk of bias assessments by study

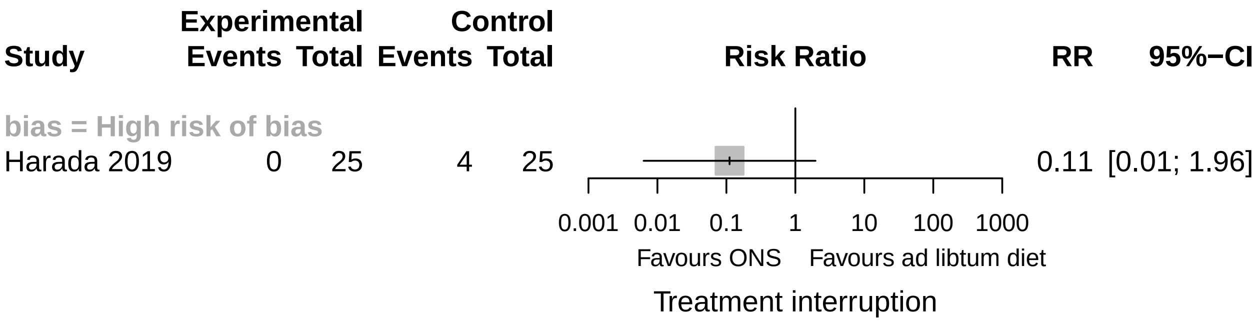
```
rob_traffic_light(rob_mort_3, tool = "ROB2", colour = "colourblind", psize = 10)
```



## 6.2 Interruption of treatment

### 6.2.1 Forest plot

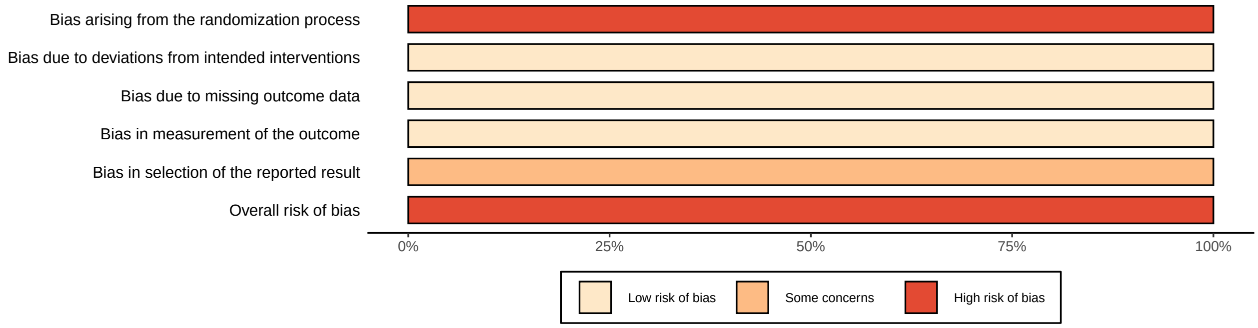
```r
int_3 <- metabin(
  HNC$event.e,
  HNC$n.e,
  HNC$event.c,
  HNC$n.c,
  sm = "RR",
  method = "MH",
  RR.cochrane = TRUE,
  MH.exact = FALSE,
  allstudies = TRUE,
  HNC$studlab,
  subset = HNC$outclab == "Interruption of anti-cancer treatment" & HNC$C == 3,
  byvar = HNC$bias,
  comb.fixed = FALSE,
)

int_3_d <- data.frame(int_3)
rob_int_3 <- merge(rob_int_3, int_3_d[,c("w.random", "studlab")], by = "studlab", all = TRUE)

forest(int_3,
       xlab="Treatment interruption",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 2,
       digits.se = 1,
       comb.fixed = FALSE,
       #overall = FALSE,
       #subgroup = FALSE,
       xlim = c(0.001, 1000),
       #xlim    = "s",
       #plotwidth = "2cm",
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = TRUE,
       #pooled.events = TRUE,
       #resid.hetstat = FALSE,
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = C1,
       label.left = I1,
       fs.axis = 10,
       fs.lr = 10
)
```



### 6.2.2 Proportion of information at each level of risk of bias

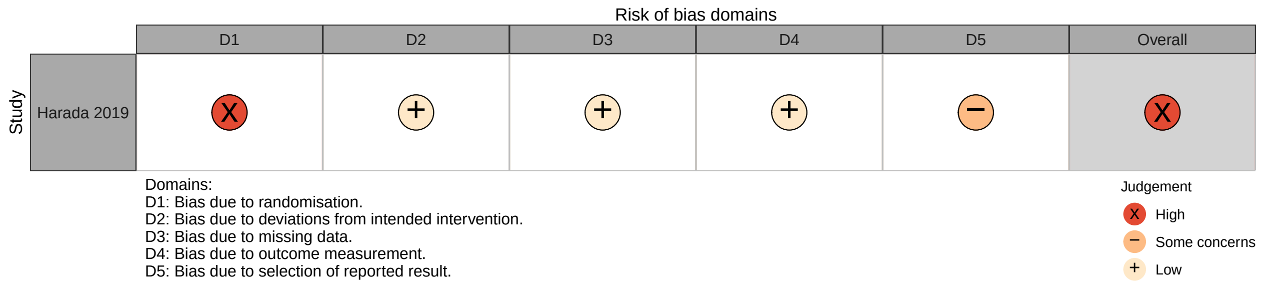
Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)

```r
rob_summary(rob_int_3, tool = "ROB2", weighted = FALSE, overall = TRUE, colour = "colourblind")
```



### 6.2.3 Risk of bias assessments by study

```r
rob_traffic_light(rob_int_3, tool = "ROB2", colour = "colourblind", psize = 10)
```

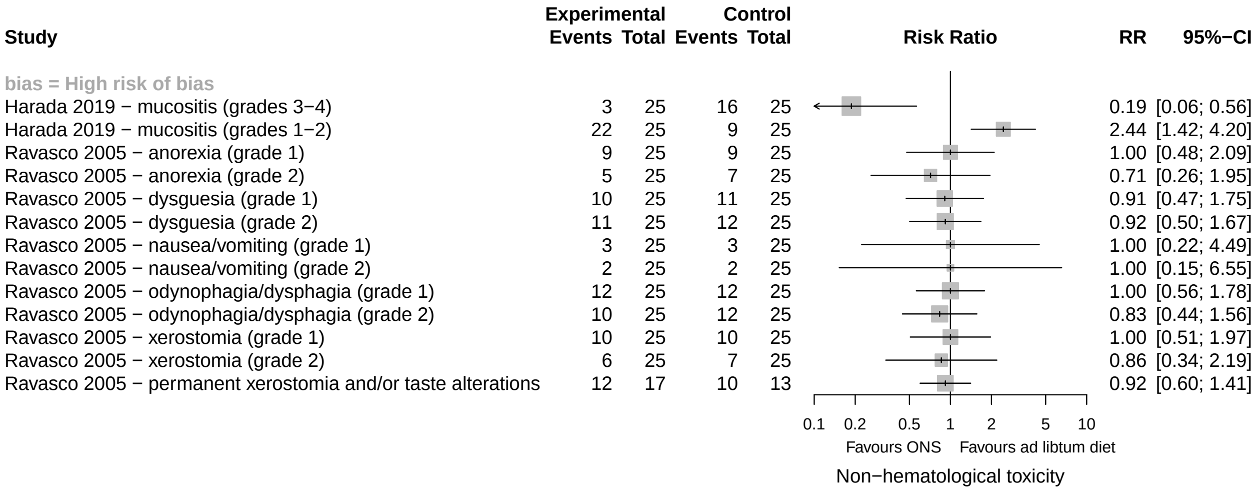


## 6.3 Summary of non-hematological toxicity outcomes

### 6.3.1 Forest plot

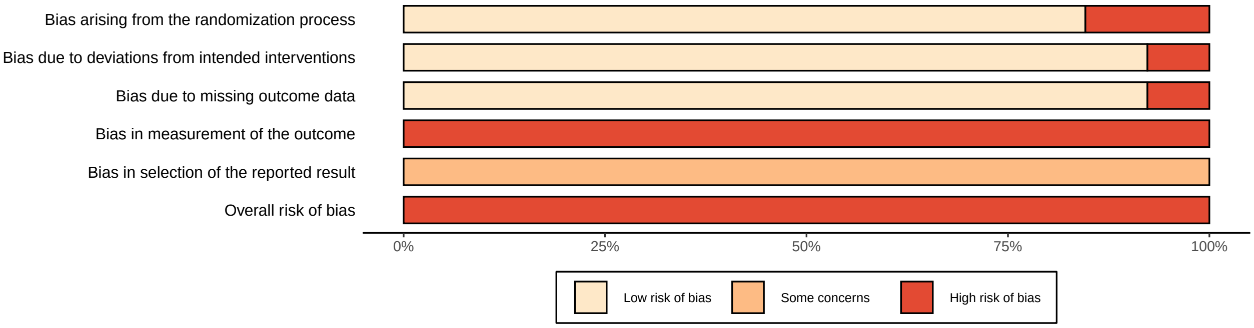
```r
tol_3 <- metabin(
  HNC$event.e,
  HNC$n.e,
  HNC$event.c,
```

```
  HNC$n.c,
  sm = "RR",
  method = "MH",
  RR.cochrane = TRUE,
  MH.exact = FALSE,
  #allstudies = TRUE,
  HNC$studlab,
  subset = HNC$outclab == "Tolerance" & HNC$C == 3,
  byvar = HNC$bias,
  comb.fixed = FALSE,
  comb.random = FALSE,
)

forest(tol_3,
       xlab="Non-hematological toxicity",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 2,
       digits.se = 1,
       comb.fixed = FALSE,
       #overall = FALSE,
       #subgroup = FALSE,
       xlim = c(0.1, 10),
       #plotwidth = "2cm",
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = C1,
       label.left = I1,
       fs.axis = 10,
       fs.lr = 10
)
```



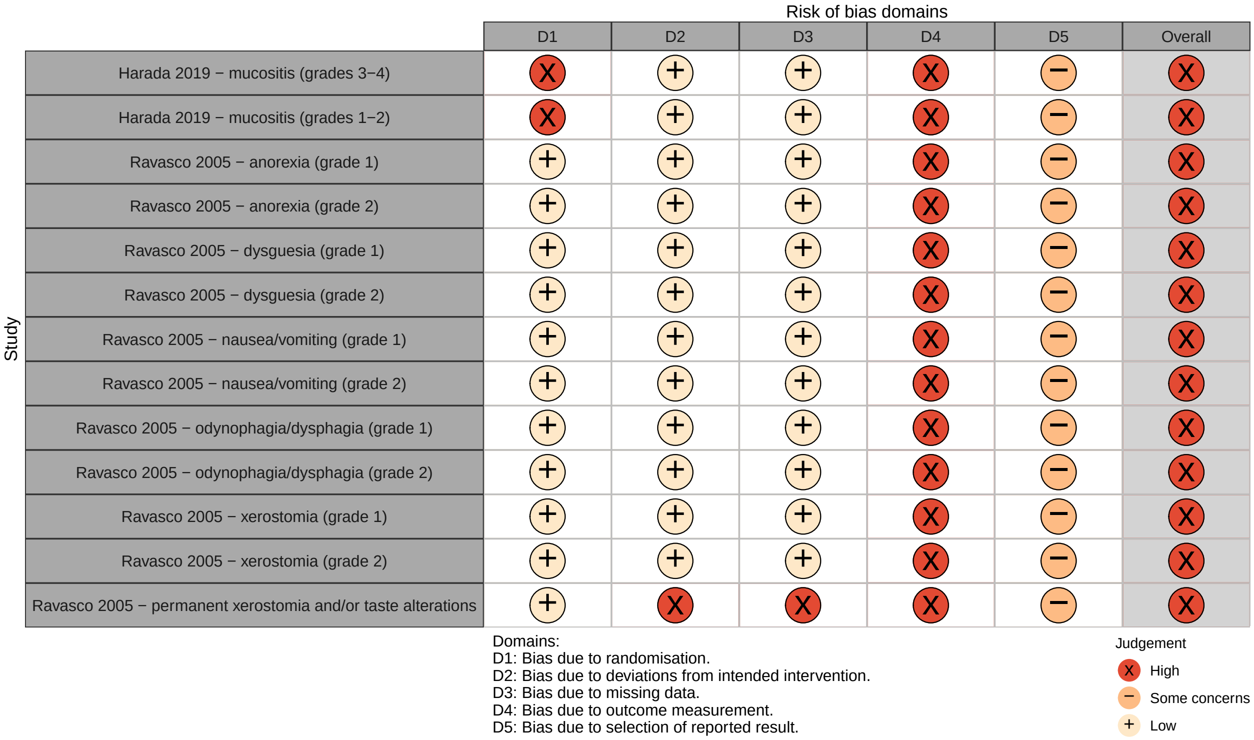
### 6.3.2 Proportion of the summary at each level of risk of bias

```
rob_summary(rob_tol_3, tool = "ROB2", weighted = FALSE, overall = TRUE, colour = "colourblind")
```



### 6.3.3 Risk of bias assessments by study

```
rob_traffic_light(rob_tol_3, tool = "ROB2", colour = "colourblind", psize = 10)
```



Risk of bias domains

| Study | D1 | D2 | D3 | D4 | D5 | Overall |
|---|---|---|---|---|---|---|
| Harada 2019 − mucositis (grades 3−4) | X | + | + | X | − | X |
| Harada 2019 − mucositis (grades 1−2) | X | + | + | X | − | X |
| Ravasco 2005 − anorexia (grade 1) | + | + | + | X | − | X |
| Ravasco 2005 − anorexia (grade 2) | + | + | + | X | − | X |
| Ravasco 2005 − dysguesia (grade 1) | + | + | + | X | − | X |
| Ravasco 2005 − dysguesia (grade 2) | + | + | + | X | − | X |
| Ravasco 2005 − nausea/vomiting (grade 1) | + | + | + | X | − | X |
| Ravasco 2005 − nausea/vomiting (grade 2) | + | + | + | X | − | X |
| Ravasco 2005 − odynophagia/dysphagia (grade 1) | + | + | + | X | − | X |
| Ravasco 2005 − odynophagia/dysphagia (grade 2) | + | + | + | X | − | X |
| Ravasco 2005 − xerostomia (grade 1) | + | + | + | X | − | X |
| Ravasco 2005 − xerostomia (grade 2) | + | + | + | X | − | X |
| Ravasco 2005 − permanent xerostomia and/or taste alterations | + | X | X | X | − | X |

Domains:
D1: Bias due to randomisation.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing data.
D4: Bias due to outcome measurement.
D5: Bias due to selection of reported result.

Judgement
X High
− Some concerns
+ Low

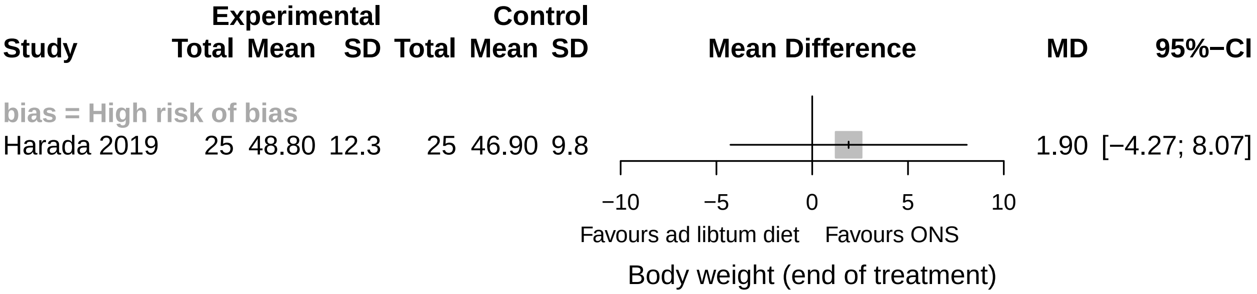
```
#labbe.metabin(x = tol_1,
#              bg = "grey",
#              studlab = TRUE,
#              comb.random = FALSE,
#              cex.studlab = 0.4)
```

## 6.4 Body weight (end of treatment)

### 6.4.1 Forest plot

```
bw_3_1 <- metacont(
  HNC$n.e,
```

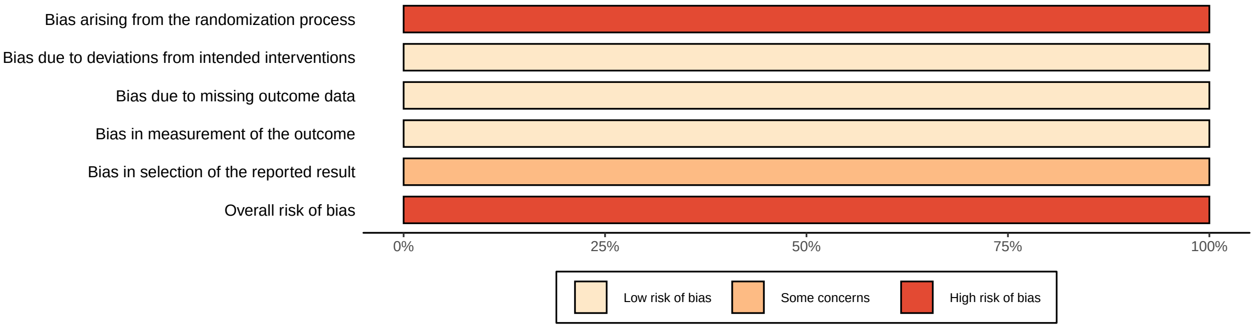
```
  HNC$mean.e,
  HNC$sd.e,
  HNC$n.c,
  HNC$mean.c,
  HNC$sd.c,
  HNC$studlab,
  data = HNC,
  subset = HNC$outclab == "Body weight" & HNC$C == 3,
  byvar = HNC$bias,
)

bw_3_1_d <- data.frame(bw_3_1)
rob_bw_3_1 <- merge(rob_bw_3_1, bw_3_1_d[,c("w.random", "studlab")], by = "studlab", all = TRUE)

forest(bw_3_1,
       xlab="Body weight (end of treatment)",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 2,
       digits.se = 1,
       comb.fixed = FALSE,
       xlim = c(-10, 10),
       #leftcols = c("studlab", "n.e", "n.c", "TE", "seTE", "random.w"),
       #xlim    = "s",
       #plotwidth = "2cm",
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = TRUE,
       #pooled.events = TRUE,
       #resid.hetstat = FALSE,
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = I1,
       label.left = C1,
       fs.axis = 10,
       fs.lr = 10
)
```



### 6.4.2 Proportion of information at each level of risk of bias

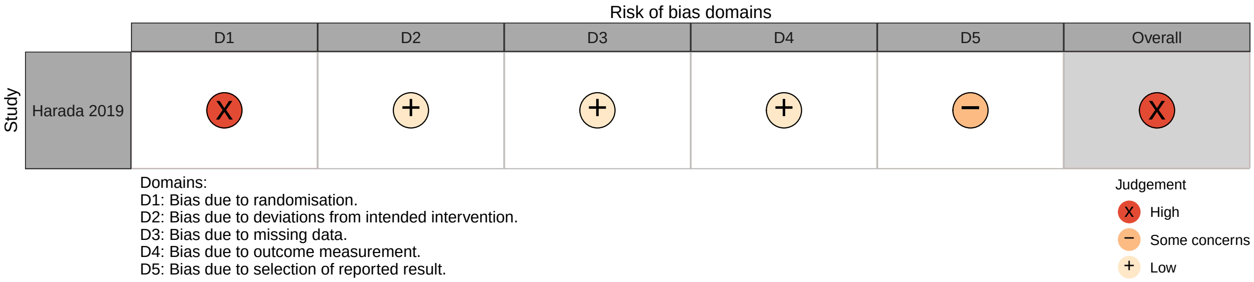
Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)

```
rob_summary(rob_bw_3_1, tool = "ROB2", weighted = FALSE, overall = TRUE, colour = "colourblind")
```



### 6.4.3 Risk of bias assessments by study

```
rob_traffic_light(rob_bw_3_1, tool = "ROB2", colour = "colourblind", psize = 10)
```



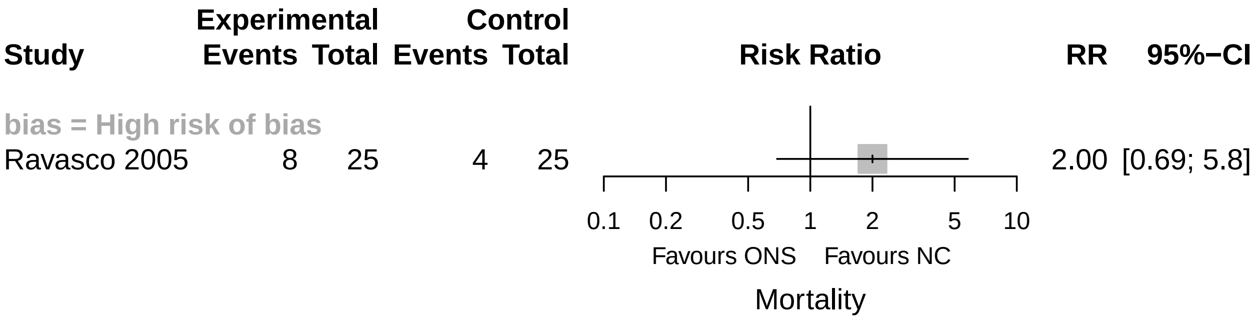
# 7 Comparison 4

## 7.1 Mortality

### 7.1.1 Forest plot

```
mort_4 <- metabin(
  HNC$event.e,
  HNC$n.e,
  HNC$event.c,
  HNC$n.c,
  sm = "RR",
  method = "MH",
  RR.cochrane = TRUE,
  MH.exact = FALSE,
  allstudies = TRUE,
  HNC$studlab,
  subset = HNC$outclab == "Mortality" & HNC$C == 4,
  byvar = HNC$bias,
  comb.fixed = FALSE,
)

forest(mort_4,
```

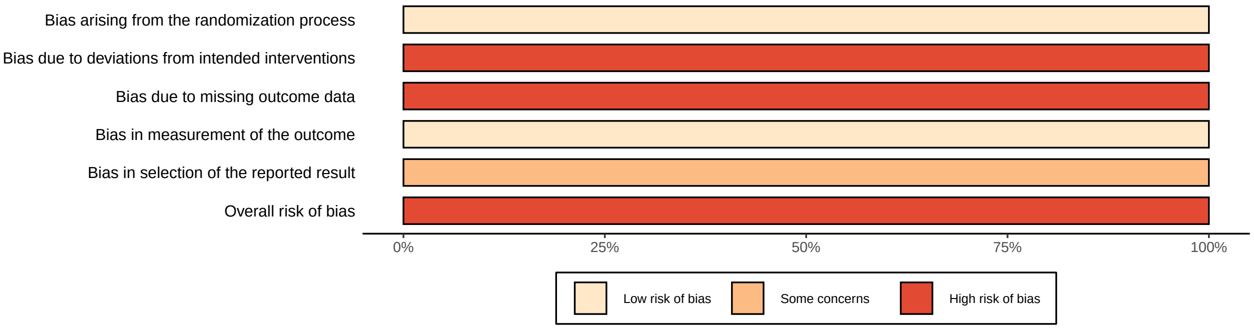
```
       xlab="Mortality",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 2,
       digits.se = 1,
       comb.fixed = FALSE,
       #overall = FALSE,
       #subgroup = FALSE,
       xlim = c(0.1, 10),
       #xlim    = "s",
       #plotwidth = "2cm",
       subgroup = FALSE,
       hetstat = FALSE,
       overall.hetstat = TRUE,
       #pooled.events = TRUE,
       #resid.hetstat = FALSE,
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = C1,
       label.left = I1,
       fs.axis = 10,
       fs.lr = 10
)
```



### 7.1.2 Proportion of information at each level of risk of bias

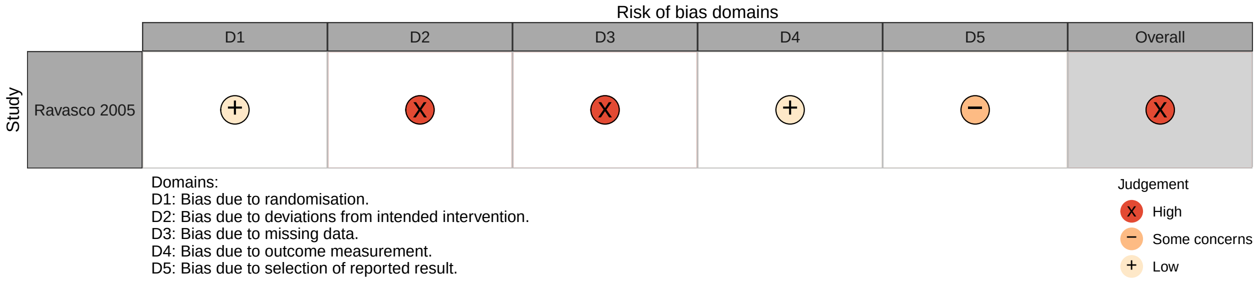
Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)

```
rob_summary(rob_mort_4, tool = "ROB2", weighted = FALSE, overall = TRUE, colour = "colourblind")
```



### 7.1.3 Risk of bias assessments by study

```
rob_traffic_light(rob_mort_4, tool = "ROB2", colour = "colourblind", psize = 8)
```

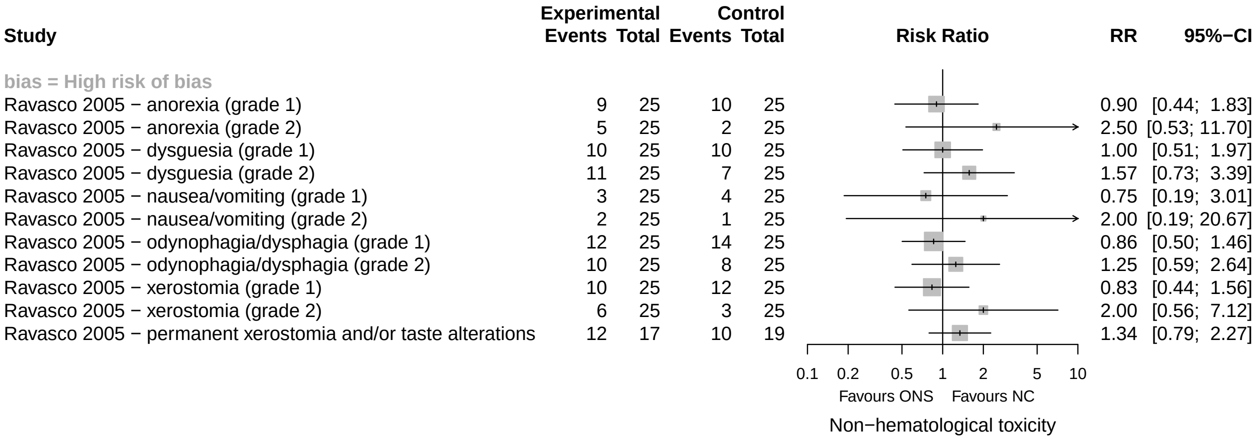


## 7.2 Summary of non-hematological toxicity outcomes

### 7.2.1 Forest plot

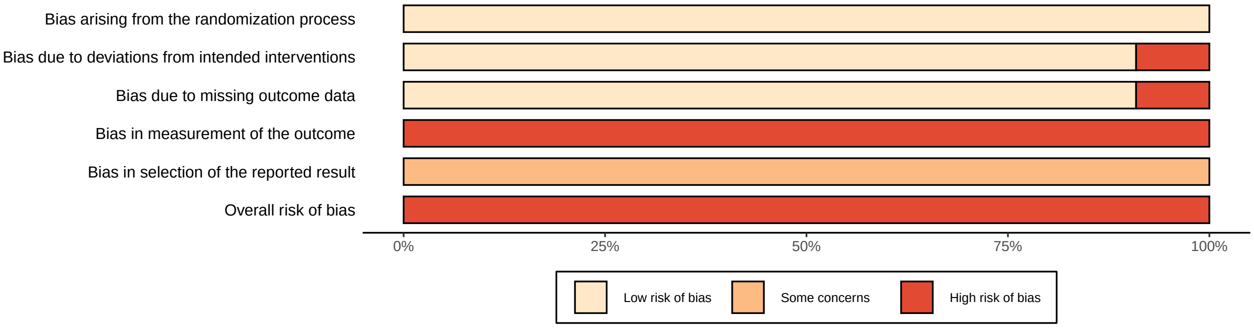
```
tol_4 <- metabin(
  HNC$event.e,
  HNC$n.e,
  HNC$event.c,
  HNC$n.c,
  sm = "RR",
  method = "MH",
  RR.cochrane = TRUE,
  MH.exact = FALSE,
  #allstudies = TRUE,
  HNC$studlab,
  subset = HNC$outclab == "Tolerance" & HNC$C == 4,
  byvar = HNC$bias,
  comb.fixed = FALSE,
  comb.random = FALSE,
)

forest(tol_4,
       xlab="Non-hematological toxicity",
       #ref = 10,
       #layout = "Revman5",
       layout = "meta",
       digits = 2,
       digits.se = 1,
       comb.fixed = FALSE,
       #overall = FALSE,
       #subgroup = FALSE,
       xlim = c(0.1, 10),
       #lim = "s",
       #plotwidth = "2cm",
       colgap.forest = "0.5 cm",
       just = "right",
       label.right = C1,
       label.left = I1,
```

```
       fs.axis = 10,
       fs.lr = 10
)
```



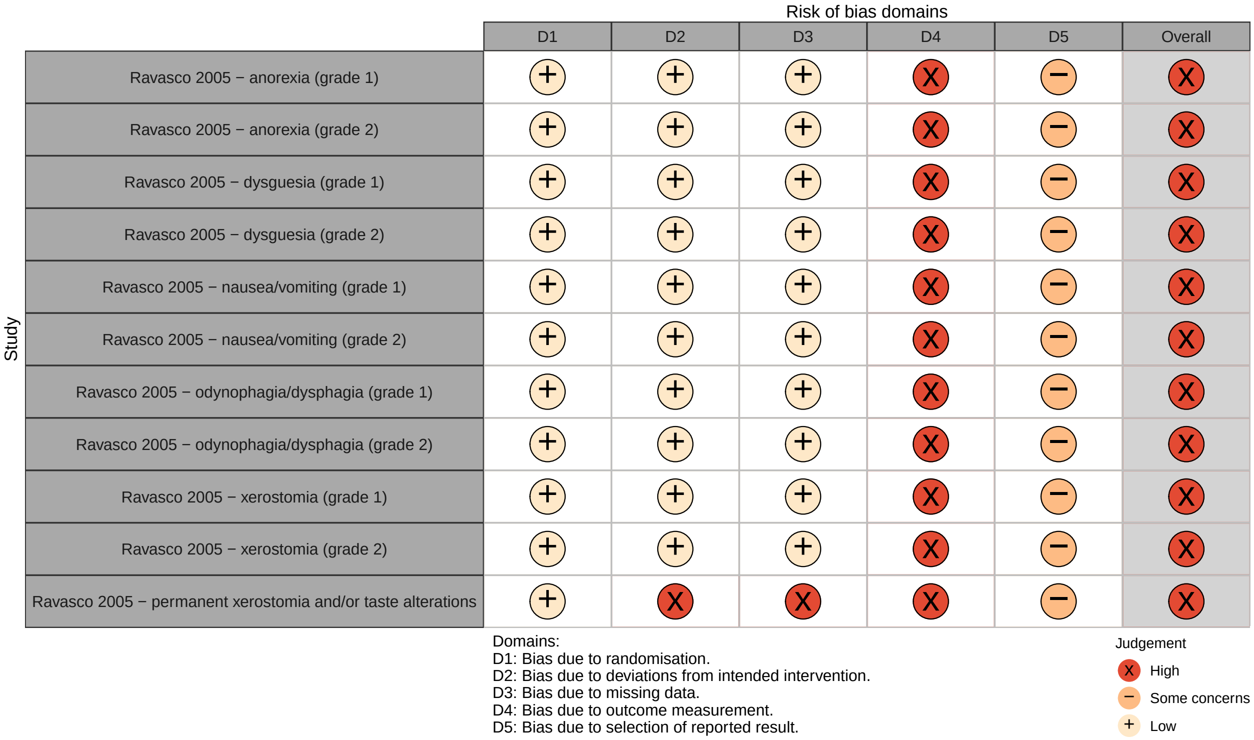
### 7.2.2 Proportion of the summary at each level of risk of bias

```
rob_summary(rob_tol_4, tool = "ROB2", weighted = FALSE, overall = TRUE, colour = "colourblind")
```



### 7.2.3 Risk of bias assessments by study

```
rob_traffic_light(rob_tol_4, tool = "ROB2", colour = "colourblind", psize = 10)
```



Risk of bias domains

| Study | D1 | D2 | D3 | D4 | D5 | Overall |
|---|---|---|---|---|---|---|
| Ravasco 2005 − anorexia (grade 1) | + | + | + | X | − | X |
| Ravasco 2005 − anorexia (grade 2) | + | + | + | X | − | X |
| Ravasco 2005 − dysguesia (grade 1) | + | + | + | X | − | X |
| Ravasco 2005 − dysguesia (grade 2) | + | + | + | X | − | X |
| Ravasco 2005 − nausea/vomiting (grade 1) | + | + | + | X | − | X |
| Ravasco 2005 − nausea/vomiting (grade 2) | + | + | + | X | − | X |
| Ravasco 2005 − odynophagia/dysphagia (grade 1) | + | + | + | X | − | X |
| Ravasco 2005 − odynophagia/dysphagia (grade 2) | + | + | + | X | − | X |
| Ravasco 2005 − xerostomia (grade 1) | + | + | + | X | − | X |
| Ravasco 2005 − xerostomia (grade 2) | + | + | + | X | − | X |
| Ravasco 2005 − permanent xerostomia and/or taste alterations | + | X | X | X | − | X |

Domains:
D1: Bias due to randomisation.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing data.
D4: Bias due to outcome measurement.
D5: Bias due to selection of reported result.

Judgement
X High
− Some concerns
+ Low